American Heart Journal

Contents

continued on page 7

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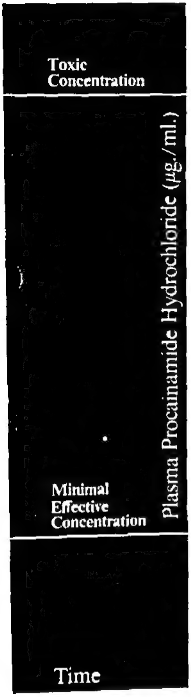

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Contents *continued*

continued on page 9

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continued on page 9

Contents *continued*

September 1976

American Heart Journal

Contents

continued on page 7

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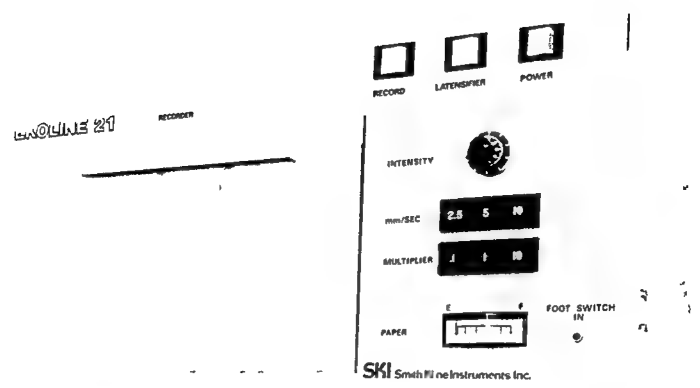
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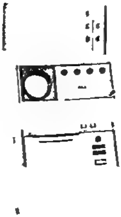

September 1976

American Heart Journal

Contents

continued on page 7

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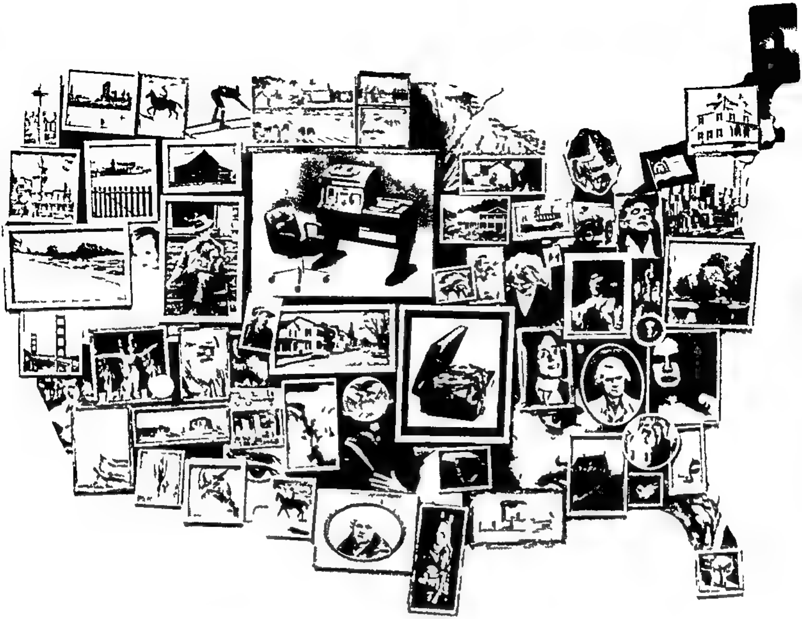

continued on page 9

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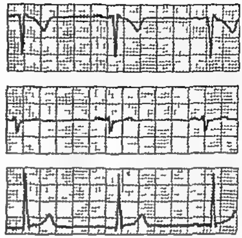

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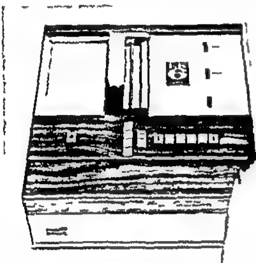

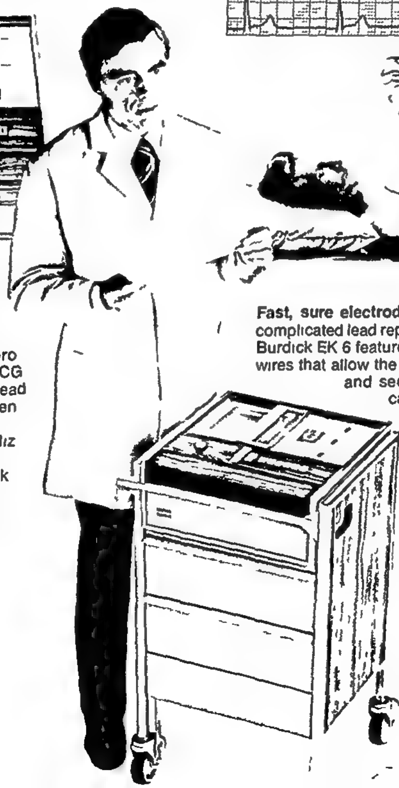

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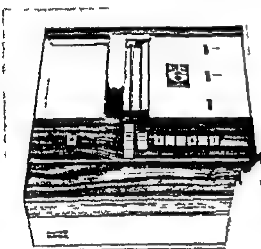

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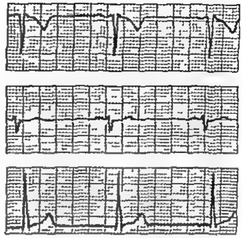

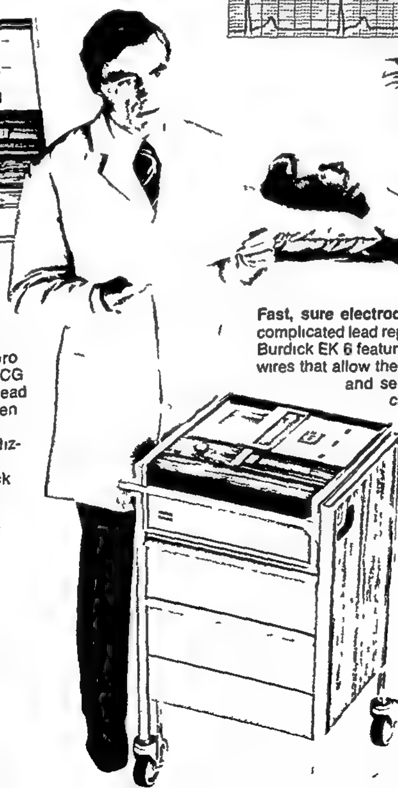

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Contents *continued*

Contents *continued*

October 1976

American Heart Journal

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Contents

continued on page 7

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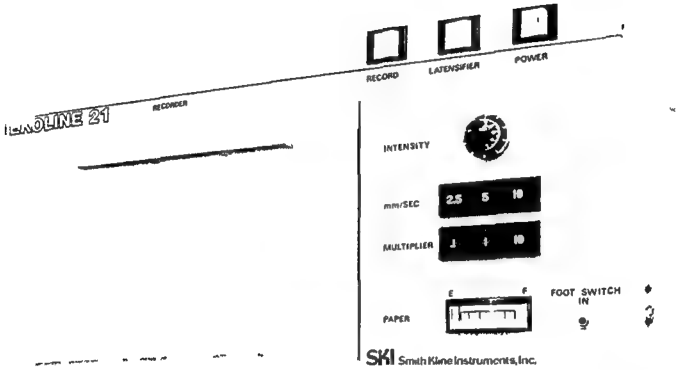
continued on page 9

Contents *continued*



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Contents

continued on page 7

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continued on page 9

Contents *continued*

American Heart Journal

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Contents

continued on page 7

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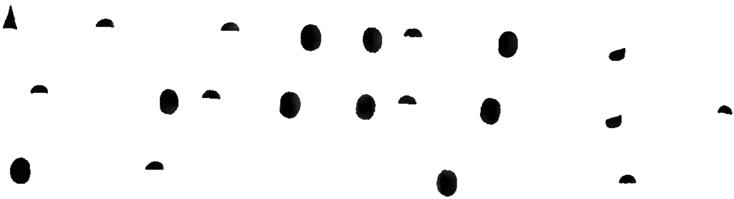

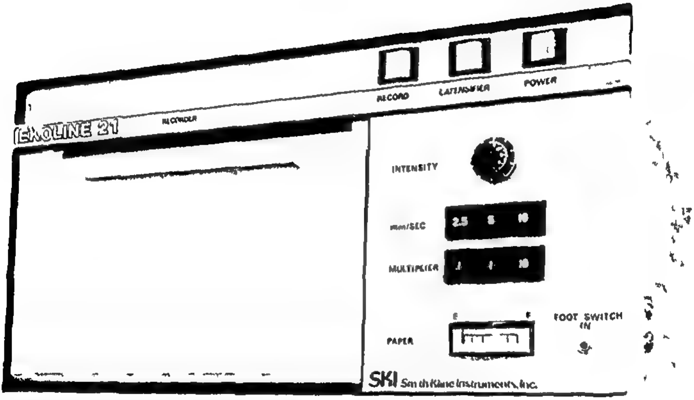
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Contents

continued on page 7

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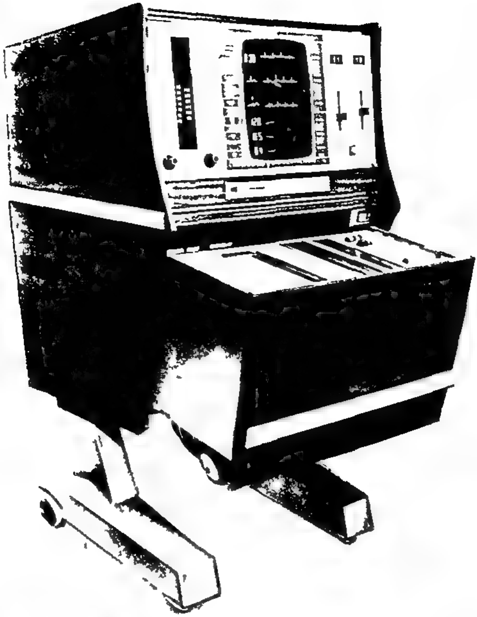

continued on page 9

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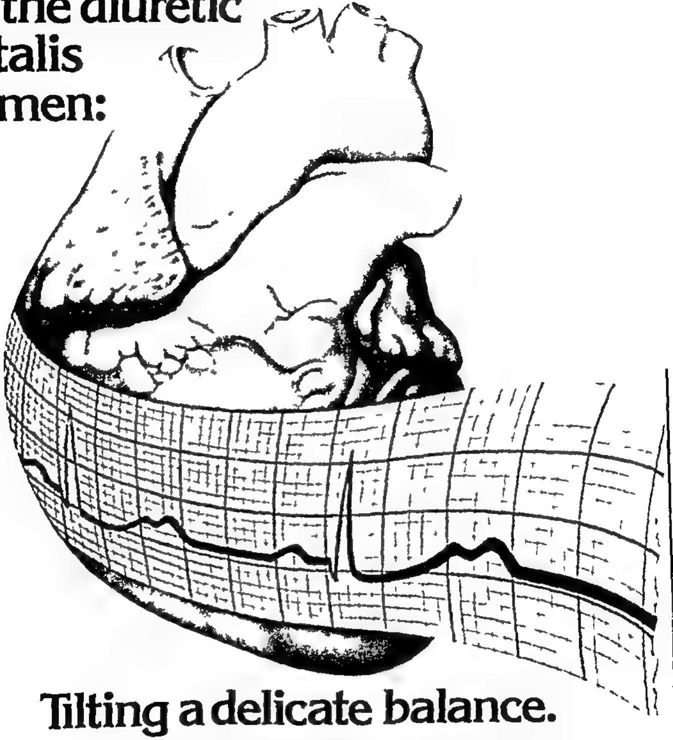

Tilting a delicate balance.

Certain diuretics such as thiazides, furosemide, and ethacrynic acid may remove potassium and the resulting potassium deficit can rapidly trigger arrhythmias in the digitalized patient Of course, potassium supplements should not be administered with any potassium-sparing diuretics such as spironolactone and triamterene

American Heart Journal

August 1976 Volume 92 Number 2

Editorial

Classification of Truncus Arteriosus Communis (TAC)

Richard Van Praagh, M.D.
Boston, Mass.

I would like to thank Dr. Jesse Edwards for his kind comments concerning our paper and for his interesting suggestions concerning the classification of TAC. These proposals from one of the all time grand masters of cardiac pathology merit careful consideration by serious students of congenital heart disease.

I am delighted that Dr. Edwards agrees that type 4 of Collett and Edwards[2] really is not a form of TAC (but a solitary aortic trunk with absence of the pulmonary trunk) and that there is no essential difference between Collett and Edwards'[2] types 2 and 3. They are the same as type A2 of Van Praagh and Van Praagh,[3] this being the classification of TAC that was employed by Calder and associates (please see Fig. 1).

To my mind, Dr. Edwards' most interesting proposals were (1) to exclude from the category of TAC all cases without a ventricular septal defect (VSD) and with two semilunar valve rings, instead calling such cases AP window, and (2) to regard all other anatomic variations, such as absence of a pulmonary artery branch or interruption of the aortic arch, merely as associated malformations rather than as separate types of TAC as in the classification of Van Praagh and Van Praagh.

This is essentially the conclusion reached in 1963 primarily on clinical grounds by Tandon, Hauck, and Nadas. There would then be only two forms of truncus, type 1 and type 2. This would certainly simplify the classification of TAC. It would do away with Collett and Edwards' types 3, 4, and 5, and it would render unnecessary all of Van Praagh and Van Praagh's[3] types B, as well as our types A3 and A4. Moreover, as Dr. Edwards correctly observes, type 1 shades into type 2 (we jokingly refer to these in between cases as type 1½), making one wonder whether or not any classification of TAC is really necessary. Why not dispense with all classification of TAC? One certainly could.

However, my own view is that a classification, while certainly not strictly necessary, is nonetheless a convenient form of shorthand. A good classification, by including the main anatomic types, helps to let one know what occurs, what to expect, and what to look for.

Ten years ago, when we were attempting to understand what TAC really is from the anatomic and embryologic standpoints, we realized that there were three deficiencies in the classification of Collett and Edwards.[2] As mentioned above, their types 2 and 3 are essentially the same thing, type 4 is not a form of TAC, and there is no way of designating those rare cases of TAC without a VSD. This was why we felt it would be helpful to present a classification[3] of TAC that would be able to encompass all known anatomic types, including cases without a VSD.

Another way of handling the problem of TAC

From the Children's Hospital Medical Center, Boston, Mass.

Received for publication Oct. 17, 1975.

Reprint requests: Dr. Richard Van Praagh, The Children's Hospital Medical Center, 300 Longwood Ave., Boston, Mass. 02115.

with an intact ventricular septum is to deny that such cases really are examples of TAC One may call them something else, such as large aortico pulmonary (AP) window, as Dr Edwards sug gests Certainly there is no doubt that huge AP window, recently termed "aortopulmonary septal absence by Daily and associates,[5] is anatomi cally distinctly different from typical TAC The main difference is that in classical TAC there is only one semilunar valve ring, whereas in large AP window there are two semilunar valve rings

Then, in an effort to validate this distinction between large AP window and TAC, Dr Edwards reminds us of the generally accepted definition of TAC one great artery arising from the base of the heart giving rise to the coronary arteries (I would add at least one), the pulmonary arteries (at least one) and the systemic circulation The point that Dr Edwards seeks to make is that TAC is defined as *one* great artery, whereas large AP window has *two* semilunar valves and therefore in this line of reasoning does not qualify as a form of TAC

I wish this argument were really convincing because then the problem of TAC without VSD could be solved in this way, thereby simplifying the understanding and classification of TAC *Unfortunately* however, one cannot be too insist ent about TAC being only *one* great artery in any literally accurate sense, because the essential concept and therefore the defining criterion of TAC is that it is two great arteries, the aorta and main pulmonary artery that are largely undi vided or in common TAC is one great artery only in the sense that the aorta and the main pul monary artery are largely not separated from each other

Why is large AP window not a pure form of TAC perhaps the only form of TAC in which there is nothing else wrong? Certainly the aorta and main pulmonary artery are in common or if one prefers Latin, *truncus arteriosus communis* surely is present

Let us consider some analogies If the atrial septum is absent, we call this common atrium, despite the fact that there may be two atrioven tricular (AV) valves or a common AV valve If the ventricular septum is absent, we call this common ventricle, whether or not there are two AV valves or a common AV valve Similarly, if the aortico pulmonary septum is absent why shouldn t we call this common arterial trunk (*truncus arterio sus communis*), whether there are one or two semilunar valves? I think we should, in the *interests of anatomic accuracy*

In classical TAC, the malformation that often is associated with a large AP septal defect is thought to be atresia of the subpulmonary infun dibulum This in turn results in the typical VSD, and in partial or complete absence of the pulmonary valve leaflets In other words, clas sical TAC appears to be much more than common great arteries We concluded[4] that typical TAC is pseudotruncus (tetralogy of Fallot with pulmonary infundibular atresia) with partial or complete absence of the pulmonary valve, and with partial or complete absence of the aorticopulmonary septum The morphology of the right ventricular outflow tract in pseudo truncus (tetralogy with pulmonary outflow tract atresia) and in true TAC is virtually identical In both the parietal band (conal septum) appears to be fused with the conal free wall and often is difficult to identify with certainty We found we couldn t tell a pseudo truncus' from a 'true truncus without looking at the great arteries In this way we were led to the unexpected conclusion that classical TAC *and tetralogy of Fallot are first cousins' —close* ly interrelated anomalies

Dr Josef Warkany, the eminent teratologist, told me that he has found that the thalidomide babies are dying of congenital heart disease and that of the anomalies of the great arteries, two kinds predominate tetralogy of Fallot and TAC This also was documented by Keck and asso ciates[6] These findings suggest that there is a biological, as well as a morphological, relationship between tetralogy and TAC The high incidence of right aortic arch and of abnormal locations of the coronary ostia in both also supports this interpretation Hence it appears that pseudo truncus (extreme tetralogy) occasionally can have an AP septal defect that extends down to the semilunar valve level and when it does we call this combination of anomalies classical TAC

One of the more important problems concern ing the understanding of TAC is that there seems to be no such thing as true truncus arteriosus as classically conceived (all is pseudo!) The classical concept is that TAC is due to a failure of down growth of the aorticopulmonary septum result

ing in lack of division of the great arteries semilunar valves and ventricular *outflow tracts* If this concept were correct it would be impossible to have absence of the AP septum associated with divided semilunar valves and an intact ventricular septum but this does indeed occur[1 2 3]

The classical concept of TAC appears to be half right and half wrong It is true that there is a defect of the aorticopulmonary septum However the semilunar valve in classical TAC appears not to be the common (undivided) truncal valve of the embryo but the aortic valve with or without a remnant of the pulmonary valve[3] The pulmonary valve has been partially or totally obliterated by the subpulmonary infundibular atresia the pulmonary valve being the back door of the subpulmonary infundibulum The VSD is not a defect of or within the conal septum Rather as in extreme tetralogy the truncal VSD is a large hole above the ventricular septum and septal band Normally this space is filled by the well expanded subpulmonary conus (parietal band or conal septum) But in classical TAC as in extreme tetralogy this space is wide open because the atretic infundibulum is very small and the conal septum (parietal band) is fused with the conal free wall

In TAC why is the infundibulum not absent instead of atretic? If the subpulmonary conus were absent in TAC as it is in typical transposition of the great arteries (TGA) then the pulmonary valve leaflets would be well formed (instead they are partially *or totally absent*)[3] and there would be pulmonary-mitral fibrous continuity in TAC as there is in typical TGA However in classical TAC I have *never observed* fibrous continuity *between* the pulmonary leaflet remnant and the mitral valve Hence in classical TAC we think the subpulmonary infundibulum must be atretic not absent

Amid the heterogeneity of the several different malformations that are called TAC there seems to be only one common denominator a relatively large defect of the AP septum that extends down to the semilunar valve level This is why I do not think it is advisable to exclude large AP window from the category of TAC Indeed this appears to be the only pure form of TAC that occurs without the frequently associated anomalies of the subpulmonary conus and pulmonary valve It is noteworthy that Dr Edwards refers to large AP window as a partial form of TAC So he too really does not exclude it from the category of TAC

To say that absence of the AP septum is just a large AP window and not a form of TAC is considered to be an exercise in semantics because no matter what words are used when the aorticopulmonary septum is absent the great arteries are truly undivided or in common At the risk of a pun it may be said that Dr Jesse Edwards and I are not semanticists at heart! Our common concern is that *terminology accurately reflect* what Dr Ed Lambert used to call the dirty little facts!

But one may still object A large AP window is not what most people mean by TAC! This is true Since it is much commoner to encounter the complicated forms of TAC (with conal and pulmonary valvular anomalies in addition to a large AP septal defect) people naturally associate the common forms with what TAC *really* is People naturally tend to associate the most frequent forms with being the real thing (with apologies to the Coca Cola Company!) This is a frequency effect

The real thing in TAC is that the aorta and pulmonary artery are in common—not separated This is the basic meaning of the concept of TAC and hence the essential defining criterion All else are variables of greater or lesser frequency

To summarize I have no objection whatever to calling absence of the aorticopulmonary septum a large AP window because it is I would object to the assertion that a large AP window is not a *form* of TAC because it is I would fully agree that absence of the AP septum is very different from the typical (most frequent) form of TAC this being reflected in all serious anatomic classifications[2 3]

Although I am aware of no reason to alter or abandon our classification of TAC[3] I am not laboring under the delusion that it is necessarily the be all end all here On the contrary the only constant we know is change Let us briefly consider the question *How many types of TAC are there really?* By types I mean anatomically and embryologically significantly different diseases TAC certainly seems to be a phenotype not a genotype Let us try to list the really different or basic types of TAC (The following is not

intended as yet another anatomic classification of TAC! Rather, it is an approach to a more basic, developmental understanding)

1 *The large aortic arch type of TAC (anatomic types A1, A2 A3)*[3] We think this form is characterized by subpulmonary infundibular atresia, partial or complete absence of the pulmonary valve leaflets, partial or complete absence of the AP septum occasionally associated with absence of a pulmonary artery branch and often with a right aortic arch This is the classical (most frequent) form of TAC There is a large fourth arterial arch and a small sixth arterial arch the aortic arch being large and the ductus arteriosus being small or absent

2 *The interrupted aortic arch type of TAC (anatomic types A4 and B4)*[3] This form may be a significantly different anomaly than the foregoing, rather than merely another associated malformation The TAC appears to be composed mainly of the pulmonary trunk, rather than predominantly of the aorta as in the preceding form Is subpulmonary infundibular atresia present in the interrupted aortic arch type? It may well be, but I am not certain Although the right ventricular outflow tract region looks essentially the same as in the previous form it is difficult to reconcile the concept of infundibular atresia on the one hand with a large pulmonary trunk on the other In this form there is a *small* fourth arterial arch and a large sixth arterial arch The aortic arch displays hypoplasia preductal coarctation atresia or interruption and the ductus arteriosus is huge It is intriguing and still totally mysterious why the development of the aortic arch and ductus arteriosus varies inversely[3] in these first two basic types of TAC while the anatomy at the ventricular and semilunar valve levels appears to be essentially identical

3 *The large AP window type of TAC (anatomic types B2 and B4)*[3] Absence of the AP septum can be isolated or it can be associated with interrupted aortic arch[5] or with aortic valvular atresia[7] Conal atresia with consequent absence (partial or complete) of the pulmonary valve leaflets is not present hence two semilunar valve rings are characteristic Typically, the ventricular septum is intact

4 *The transposition type of TAC (anatomic type A2)*[3] A complete muscular subtruncal conus is present precluding truncal–atrioventricular fibrous continuity, and the truncus arises anteriorly, entirely above the right ventricle (unpublished observations) This rare form has been described by Bharati and associates[8] and is considered to reflect failure of absorption of the subaortic conus Thus, although TAC occurs almost always in association with a normally related (nontransposed) type of conotruncus rarely TAC *can* occur with a transposed type of conotruncus

In closing it should be emphasized that we have doubtless much to learn concerning the morphogenesis of the various forms of TAC and virtually everything to learn about their etiologies I would again like to thank Dr Jesse Edwards for his stimulating commentary

REFERENCES

1 Calder L Van Praagh R Van Praagh S Sears W P Corwin R Levy A Keith J D and Paul M H Truncus arteriosus communis Clinical angiocardiographic and pathologic findings in 100 patients AM HEART J 92 23 1976

2 Collett R W and Edwards J E Persistent truncus arteriosus a classification according to anatomic types *Surg Clin North Am* 29 1245 1949

3 Van Praagh R and Van Praagh S The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications A study of 57 necropsied cases Am J Cardiol 16 406 1965

4 Tandon R Hauck A J and Nadas A S Persistent truncus arteriosus a clinical hemodynamic and autopsy study of nineteen cases Circulation 28 1050 1963

5 Daily P O Sissman N J Lipton M J and Shumway N E Correction of absence of the aorticopulmonary septum by creation of concentric great vessels Ann Thorac Surg 19 180 1975

6 Keck E W Roloff D and Markworth P Cardiovascular findings in children with the thalidomide dysmelia syndrome Proc Assoc Europ Paediatr Cardiol 8 66 1972

7 Swift L H Shimomura S *Ryan* S *F* and Van Praagh R New type of truncus arteriosus communis with two semilunar valves aortic valvular atresia and no ventricular septal defect Circulation 40 III 199 1969

8 Bharati S McAllister H A Rosenquist G C Miller R A Tatooles C J and Lev M The surgical anatomy of truncus arteriosus communis J Thorac Cardiovasc Surg 67 501 1974

Hemodynamic effects of steroids in cardiac disease

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Recently Maroko and his co-workers observed that various therapeutic manipulations can reduce the extent of myocardial necrosis in dogs after coronary arterial occlusion. Steroids were found to be particularly effective in preserving the jeopardized myocardium. Further, the beneficial actions of steroids have been observed in man. Maley and associates[2] administered 2 gm. of methylprednisolone to 15 patients with an acute myocardial infarction. They evaluated infarct size by serial serum creatinine phosphokinase determinations and observed an apparent salvage of the myocardium.

In spite of the interest in steroids, there is still limited information on the hemodynamic effects of large dosage of corticosteroids in acute uncomplicated myocardial infarction. The following study was designed and performed to answer this unresolved question.

Methods

Studies were performed in two groups of patients: seven patients who had recently sustained an acute transmural myocardial infarction and six cardiac patients who were undergoing a diagnostic cardiac catheterization.

Acute myocardial infarction group. Hemodynamic studies were performed from 1 to 9 days after the onset of symptoms in seven patients who had an acute transmural myocardial infarction documented by a typical history, electrocardiographic (ECG) findings, and serum enzyme changes. Six of the seven patients were males. The average age of the group was 52 years. Most of the patients had received therapy, when needed, in the form of oxygen, narcotics, sedatives, diuretics, and lidocaine before the study. The procedure was carefully explained to the patient and informed consent was obtained.

Right heart catheterization was performed with a Swan-Ganz flow-directed balloon-type catheter inserted through the right antecubital vein. Arterial pressure was measured through a Cournand needle in the brachial artery. Pressures were measured with Statham transducers and recorded with the ECG on an Electronics for Medicine DR 12 machine. The left ventricular filling pressure was taken as the mean of the pulmonary capillary wedge pressure. Cardiac output was determined by the Fick technique. Mixed venous blood was obtained from the pulmonary artery and arterial blood from the brachial artery. Arterial and mixed venous oxygen contents were determined by the method of Van Slyke and Neill. Oxygen consumption was determined by measuring ventilation with a spirometer and analyzing the expired gas with a Micro-Scholander apparatus. After recording the control hemodynamic measurements, 2 gm. of methylprednisolone were infused over a 20 minute period. One hour after the termination of the infusion, the pressures and cardiac output were again measured.

Diagnostic cardiac catheterization group. A group of six hospitalized patients underwent right and, in three cases, left heart catheterizations primarily as an aid to other clinical management. The conditions of the patients are listed in Table

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REFERENCES

1 Calder L Van Praagh R Van Praagh S Sears W P Corwin R Levy A Keith J D and Paul M H *Truncus arteriosus communis Clinical angiocardiographic and pathologic findings in 100 patients* Am Heart J 92 23 1976

2 Collett R W and Edwards J E Persistent truncus arteriosus a classification according to anatomic types *Surg Clin North Am* 29 1245 1949

3 Van Praagh R and Van Praagh S The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications A study of 57 necropsied cases Am J Cardiol 16 406 1965

4 Tandon R Hauck A J and Nadas A S Persistent truncus arteriosus a clinical hemodynamic and autopsy study of nineteen cases Circulation 28 1050 1963

5 Daily P O Sissman N J Lipton M J and Shumway N E Correction of absence of the aorticopulmonary septum by creation of concentric great vessels Ann Thorac Surg 19 180 1975

6 Keck [illegible] W Roloff D and Markworth P Cardiovascular findings in children with the thalidomide dysmelia syndrome Proc Assoc Europ *Paediatr* Cardiol 8 66 1972

7 Swift L H Shimomura S Ryan S F and Van Praagh R New type of truncus arteriosus communis with two semilunar valves *aortic valvular* atresia and no ventricular septal defect Circulation 40 III 199 1969

8 Bharati S McAllister H A Rosenquist C C Miller R A Tatooles C J and Lev M The surgical anatomy of truncus arteriosus communis J Thorac Cardiovasc Surg 67 501 1974

Table II Diagnostic cardiac catheterization group

Patient No and condition	Sex age	RA (mean) (mm Hg)	RV S/D (mm Hg)	PA S/D (mm Hg)	PA (mean) (mm Hg)	Wedge mean (mm Hg)	BA S/D (mm Hg)	BA (mean) (mm Hg)	LV S/D (mm Hg)	Rate (b p.m)	A Vo diff (vol %)	Oxygen consump (c c / min./ M)	CI (L / min / M)	SI (mL/ beat/ M)	• cm	
1 Cor pulmonale																
Control	F/52	5	115/5	115/45	68	7	118/68	84	—	85	4.2	114	2 66	36	1 415	2[illegible]
Steroids		7	1 8/7	1.8/47	74	10	1?8/72	91	—	63	6.2	184	3 03	37	1 345	2.97
2. Arteriosclerotic heart disease																
Control	F/6?	2	25/2	20/8	12	5	130/70	89	130/5	115	3 6	122	3.38	29	1 235	3 588
Steroids		0	?2/0	18/6	9	2	110/60	77	110/0	115	4 1	185	4.54	45	95	3 289
3. Mitral stenosis																
Control	F/ 0	5	5/5	75/32	46	20	148/68	94	115/5	90	7 6	1?6	1 66	19	2,504	2,217
Steroids		6	100/6	100/50	66	32	130/65	86	1?0/10	61	6 9	1 8	2.58	42	1 469	2 050
4 Arteriosclerotic heart disease																
Control	M/68	1	35/1	35/15	22	13	135/68	90	—	5	5 9	123	2 07	28	2,305	2,531
Steroids		3	38/3	38/?2	?8	22	93/50	64	—	68	7 8	1 0	1.38	14	2 507	1 644
5 Idiopathic pulmonary hypertension																
Control	F/32	0	95/0	95/40	60	2	160/82	10	—	79	3 4	123	3 62	46	1 601	3 539
Steroids		0	110/0	110/50	0	4	125/68	87	—	83	5 7	126	2.21	27	2 107	2,905
6 Mitral stenosis																
Control	F/4?	1	28/1	?6/11	16	1?	140/70	93	120/2	75	4 1	144	3.52	4[illegible]	1 217	2,860
Steroids		?	25/2	25/10	15	11	135/ 0	9[illegible]	118/3	9	4	16?	3 67	45	1 238	2,583
Mean		2.3			37	9 8		93		87	4.8	125	2.81	34	1 722	2,903
values		3 0			44	13 5		83		82	5.9	169	2.90	35	1,576	2,641
p value		N S			N S	N S		N S		N S	N S	< 0.01	N S	N S	N S	N S

cent (N S) and the oxygen consumption was essentially unchanged The left ventricular filling pressure increased in six of seven patients from a mean of 13 9 mm Hg in the control period to 16 1 mm Hg during the steroid infusion The right ventricular filling pressure increased in four patients from a control value of 7 9 mm Hg to a treatment value of 10 6 mm Hg ($p < 0.05$) Steroids increased the arterial pressure from a mean of 82 to 90 mm Hg (N S) and the TTI per minute from a control of 2 416 to 2 920 mm Hg per second per minute ($p < 0.02$) On closer inspection of the data the brachial artery mean pressure rose in the six patients with an infarction older than 24 hours and fell in the one patient with a 1-day old myocardial infarction The systemic peripheral resistance was minimally decreased after the steroid infusion

At the conclusion of the hemodynamic studies Patient 7 developed severe chest pain associated with a 35 mm Hg rise in the brachial artery systolic pressure and marked ST segment elevations Nitroglycerin was administered sublingually with a resultant fall in the blood pressure to 125/70 mm Hg and a disappearance of the chest pain Steroids produced a pulsus alternans in the right ventricle and brachial artery in Patient 1

Diagnostic cardiac catheterization group After methylprednisolone infusion the average cardiac index increased minimally from 2 81 to 2 90 L per minute per square meter (N S) Four of the patients showed a rise in this parmeter and two a fall Similarly the stroke index and cardiac rate showed minimal nonsignificant changes The A V oxygen difference increased from 4 8 to 5 9 volumes per cent (N S) and the oxygen consumption also increased from 125 to 169 c c per minute per square meter ($p < 0.01$) The left ventricular filling pressure increased in four of the patients from a mean of 9.8 mm Hg in the control period to 13 5 mm Hg during the steroid infusion The right ventricular filling pressure also increased in four patients from a control value of 2 3 to a

Table I Acute myocardial infarction group

Patient No and condition	Sex age	R A (mean) (mm Hg)	R V S/D (mm Hg)	P A S/D (mm Hg)	P A (mean) (mm Hg)	Wedge mean (mm Hg)	B A S/D (mm Hg)	B A (mean) (mm Hg)	Rate (b p m)	A Vo₂ diff (vol %)	Oxygen con sump (c c / min / M²)	C I (L / min / M²)	S I (ml / beat M²)	Peri pheral resis tance (dynes sec cm⁻⁵)	TTI/ min (mm Hg sec / min)
1 Ant wall myo inf 6 days old															
Control	F/63	0	28/0	28/6	13	2	130/62	84	85	4 2	125	2 98	35	1 33?	?430
Steroids		4	27 35/4	35/15	22	13	135 142/72	94	[illegible]	4 0	135	3 36	40	1 290	?960
2 Inf wall myo inf 9 days old															
Control	M/48	7	25/7	25/12	16	12	105/62	76	88	3 9	124	3 19	36	1 000	2 400
Steroids		11	33/11	33/18	23	[illegible]	115/65	81	86	2 0	111	5 60	6?	610	?,960
3 Inf wall myo inf 3 days old															
Control	M/73	14	35/14	35/18	24	17	105/60	75	80	7 3	143	1 94	14	1 780	2 180
Steroids		14	40/14	40/22	28	18	128/72	91	75	6 3	163	2 59	34	1 620	?680
4 Ant wall myo inf 3 days old															
Control	M/47	15	40/15	40/30	33	30	100/72	81	107	4 9	100	2 00	19	1 680	?360
Steroids		15	40/15	40/17	24	16	125/80	95	107	5 2	109	2 10	20	1 860	30 0
5 Ant wall myo inf 2 days old															
Control	M/46	0	18/0	18/8	11	3	140/80	100	75	3 5	129	3 69	49	1 050	?940
Steroids		0	30/0	30/1?	20	[illegible]	150/85	107	75	5 0	[illegible]	1 96	[illegible]	1 830	33 0
6 Inf wall myo inf 1 day old															
Control	M/44	13	40/13	38/18	25	18	110/62	78	75	4 9	98	1 89	[illegible]	1 800	2 140
Steroids		18	40/18	40/20	26	20	97/50	65	72	4 2	130	3 12	44	830	1 8?0
7 Inf wall myo inf 3 days old															
Control	M/42	6	30/6	30/16	21	15	110/65	80	80	3 8	130	3 44	43	970	2 460
Steroids		12	32/12	32/18	23	18	145/75	98	88	3 0	140	4 96	54	830	3 550
Mean values		7 9			20	13 9		82	84	4 6	121	2 59	32	1 3?3	2 416
		10 6			24	16 1		90	84	4 2	118	3 38	40	1 261	?9?0
p value		< 0 05			N S	N S		N S	N S	N S	N S	N S	N S	N S	< 0 0?

II Five of the six patients were females The average age of the group was 49 years

Right heart catheterization was performed with a No 7 Goodale Lubin catheter inserted into the right antecubital vein Catheterization of the left ventricle was performed by inserting a No 8 Gensini catheter into the right femoral artery via the Seldinger approach Pressures and cardiac output were determined before and after the steroid administration as described in the acute myocardial infarction study

Calculations The systolic ejection time in milliseconds was measured from the beginning of the upstroke to the dicrotic notch of the arterial pressure recorded at 100 mm per second The tension time index (TTI) per minute in millimeters of mercury per second per minute is the product of the heart rate mean systolic arterial pressure and systolic ejection rate The systemic vascular resistance in dynes sec cm⁻⁵ was calculated from the formula mean arterial pressure × 1 332/cardiac output (milliliters per second)

The statistical significance of the difference (P value) between the control values and the steroid values was calculated with the paired t test

Results

Complete data of all 13 patients are presented in Tables I and II In addition the average values before and after the steroid infusion are listed in these tables with the statistical analysis

Acute myocardial infarction group As a result of the steroid infusion the average cardiac index increased from 2 59 to 3 38 L per minute per square meter (N S) and the stroke index increased from 32 to 40 ml per beat per square meter (N S) The arteriovenous (A V) oxygen difference decreased from 4 6 to 4 2 volumes per

in blood pressure This experience prompted us to terminate the administration of steroids to infarction patients after the first day of their illness

Steroids can still be of benefit if administered during the first day of the myocardial infarction There have been a number of studies to evaluate the beneficial effect of corticoid administration on infarct size In 1952 Chapman and his associates [3] using a dose of 3 to 7 mg per kilogram of cortisone found that corticosteroids given to dogs with experimentally induced myocardial infarction did not deleteriously affect the size of the infarction or the rate or quality of myocardial healing Johnson and colleagues[4] showed a reduction in the area of infarcts experimentally produced in dogs treated with cortisone (1 to 2 mg per kilogram) intramuscularly each day for 2 to 3 weeks after coronary ligation They also noted evidence of increased intercoronary anastomoses Two other groups could not confirm these beneficial results Similarly several clinical investigations showed a reduced mortality rate in patients with acute myocardial infarction treated with hydrocortisone whereas other studies have not confirmed this observation Libby and his co workers recently have studied the effect of 50 mg per kilogram of hydrocortisone on the size of experimental myocardial infarction in 28 dogs Using epicardial ECG s these workers showed that the average ST segment elevation and number of sites with ST elevation greater than 2 mV which are indices of the extent and magnitude of myocardial ischemic injury were relieved by hydrocortisone treatment following acute coronary arterial occlusion Twenty four hours after infarction transmural myocardial specimens were obtained for histologic and enzyme analysis They found that myocardial creatine phosphokinase activity was less depressed by steroid treatment and the areas of myocardium undergoing necrosis were diminished They concluded that pharmacological doses of hydrocortisone prevent myocardial cells from progressing to ischemic necrosis even when administration is initiated 6 hours after coronary occlusion

deMello and associates have recently reported the deleterious effects of methylprednisolone in patients with an evolving myocardial infarction They administered methylprednisolone (30 mg per kilogram) in single or multiple doses to 22 patients with an acute myocardial infarction beginning 7 hours after the initial CPK elevation These workers concluded that high doses of methylprednisolone led to an extension of the infarction in patients reflected by (1) observed serum CPK values exceeding those projected (2) persistent elevations of MB CPK and (3) exacerbations of ventricular dysrhythmia

In view of these varying results the exact role of corticosteroid therapy in human myocardial infarction still remains to be determined The development of new techniques that allow quantitation of infarct size in man together with the availability of precise hemodynamic measurement may clarify this issue

Summary

The hemodynamic effects of intravenous methylprednisolone were documented by right heart catheterization in seven patients with an acute uncomplicated transmural myocardial infarction 1 to 9 days after the onset of symptoms Intracardiac pressures brachial artery pressure and cardiac output were determined before and 1 hour after the termination of the methylprednisolone infusion Two grams of methylprednisolone were infused over a 20 minute period The brachial pressure rose from a mean of 82 to 90 mm Hg (N S) The brachial artery mean pressure fell in the one patient with a 1 day old infarction and it rose in the six patients with an older infarction from 83 to 94 mm Hg ($p < 0.01$) As the brachial artery pressure rose in one patient chest pain and marked ST segment elevation occurred which were relieved by nitroglycerin This experience promoted us to terminate the steroid study There was a nonsignificant increase in the cardiac index and wedge pressure The raise in the brachial artery pressure with an infarction older than 1 day was an unexpected finding since steroids are presumed to be vasodilating agents

REFERENCES

1 Maroko P R Kjekshus J K Sobel B E Watanobe T Covell J W Ross J Jr and Braunwald E Factors influencing infarct size following experimental coronary artery occlusion Circulation 43 67 19 1
2 Maley T Gulotta S and Morrison J Effect of methylprednisolone on predicted myocardial infarct size in man Clin Res 22 288 1974
3 Sambhi M P Weil M H and Udhoji V N Acute pharmacodynamic effects of glucocorticoids Cardiac

Treatment value of 3 0 mm Hg (N S) Steroids decreased the arterial pressure from a mean of 93 to 83 mm Hg (N S) and the TTI from a control of 2,903 to 2 641 mm Hg per second per minute (N S) The systemic peripheral resistance was minimally decreased after the steroid administration

Discussion

The present study revealed that methylprednisolone administration produced, in the patients with a recent myocardial infarction an average increase in the cardiac index, left ventricular filling pressure and mean brachial artery mean pressure In the patients without a myocardial infarction minimal increases in the cardiac index and left ventricular filling pressures were also observed however the mean brachial artery pressure fell in this group

There have been a number of hemodynamic studies evaluating corticosteroids Sambhi and his co workers[1] studied the hemodynamic effects of corticosteroids in 12 normal human subjects Following the injection of 500 mg of hydrocortisone 100 mg of prednisone or 22 mg of dexamethasone the cardiac index rose from 3 0 to 3 9 L per minute per square meter the arterial pressure changed insignificantly the peripheral resistance declined and the venous pressure was unaltered Dietzman and his associates[4] subsequently administered 30 mg of methylprednisolone per kilogram of body weight to 23 dogs with an experimentally produced myocardial infarction A significant increase in the cardiac index was observed with evidence of reduced peripheral vasoconstriction The blood pressure increased in the control surviving dogs as well as the steroid treated dogs Thus the effect of this dose of methylprednisolone on the systemic blood pressure could not be ascertained The authors concluded however that methylprednisolone is a peripheral vasodilating agent These same workers also administered 30 mg of methylprednisolone to 12 patients with recent cardiac valve replacement however they also received isoproterenol and volume replacement Thus it was not possible to evaluate the effect of steroids alone in this group deMello and his associates[3] recently administered methylprednisolone in single or multiple doses 30 mg per kilogram to 22 patients in the first day of their infarction The cardiac output, wedge pressure and systemic arterial pressures were not significantly altered

Vyden and his colleagues studied the effects of large dose corticosteroids 50 mg per kilogram of methylprednisolone intravenously, to assess which of the regional circulations benefits from the vasodilating action of steroids They administered the drug to 12 dogs with experimentally produced cardiogenic shock Ninety minutes after the steroid administration, a marked vasodilating effect on the coronary circulation was observed with a doubling of the coronary arterial blood flow The cardiac index also increased, whereas the arterial blood pressure and left ventricular end diastolic pressure were not affected These workers also reported that methylprednisolone at a concentration level up to 400 mg per liter had no effect on the contractile state of 15 isolated cat papillary muscles

Thus in our study the hemodynamic effects of steroids in the patients without a myocardial infarction were not unexpected Similarly the decline in blood pressure produced by steroids in the patient with the 1 day old myocardial infarction was compatible with the reports in the literature The increase in the systemic pressure in the six infarction patients who received steroids after the first day was an unexpected finding The rise in the systemic pressure in these six patients was highly significant ($p < 0.01$) An examination of the literature reveals that no group has administered steroids to infarct patients after the first day since it is presumed that any limitation of the infarction must be accomplished shortly after the onset of the infarction The mechanism for this blood pressure elevation is obscure since steroids are considered to be vasodilating agents Perhaps the steroids produce an augmented pressure response to sympathomimetic amines When a patient sustains a myocardial infarction the catecholamines are increased on the first day of the infarction but can increase over the ensuing 5 days Many workers have reported that steroids can augment the pressure response to catecholamines other workers have rejected this concept The raise in the systemic pressure should theoretically be associated with an increase in the myocardial oxygen consumption requirements which may be detrimental Indeed Patient 7 developed severe chest pain and ST segment elevation with the steroid induced rise

Riboflavin deficiency in infants and children with heart disease

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It has been shown that folic acid deficiency may be a complication of heart disease in adults[1] and in infants and children. Among the mechanisms advanced to explain this deficiency were gastrointestinal malabsorption and excessive urinary excretion. However, these mechanisms may also result in other vitamin deficiencies. In order to determine whether the latter do occur, we investigated in infants and children with congenital and acquired heart disease a deficiency of riboflavin, a member of the B complex of vitamins.

Subjects and methods

Thirty one children ranging in age from 1 month to 18 years were the study subjects. Twenty seven had congenital cardiac defects and four had rheumatic heart disease. Conventional x rays and 13 lead electrocardiograms were done on all patients. The 27 with congenital heart disease underwent cardiac catheterization and angiography. Erythrocyte sedimentation rate, C reactive protein, antistreptolysin O titer, serum complement, enzyme studies, stool analyses, and various cultures were done where necessary to make the diagnosis. The lesion in each case is described in Tables I and II.

The heights and weights of each child were recorded and plotted on the percentile chart developed by Dr. Harold C. Stuart for comparison of these children with the general population.

Riboflavin deficiency was determined from the estimation of the degree of saturation of erythrocyte glutathione reductase (EGR) with flavin adenine dinucleotide (FAD) by a modification of the method of Glatzle and associates. Details of this method were previously reported. The results are expressed as the activity coefficient (AC) which is a measure of the increment of EGR activity when exogenous FAD is added to the reaction mixture. Normal values range from 0.9 to 1.2. Values above 1.2 indicate deficiency in infants and children.

The prevalence of riboflavin deficiency in the children with heart disease was compared to that in a group of 100 normal infants and children of the same socioeconomic level who were free of acute or chronic infection, diarrhea, or vomiting.

Results

Eleven of the 31 children with cardiac disease had biochemical evidence of riboflavin deficiency with AC values ranging from 1.29 to 1.71 (Table I). This was a significantly higher prevalence than that in a group of normal children of the same socioeconomic status ($p < 0.005$). In the latter group 11 of 100 had biochemical evidence of riboflavin deficiency.

In each case the elevated AC values could be returned to within normal limits in 5 to 8 days when the riboflavin deficient children were given 2.4 mg of riboflavin per day orally.

Cardiac disease in study subjects. Eight of the 11 children with evidence of riboflavin deficiency had congenital heart disease: four with ventricular septal defect, one with ventricular septal defect with aortic insufficiency, two with tetralogy of Fallot, and one with tricuspid atresia. Three had rheumatic heart disease with mitral

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output and related hemodynamic changes in normal subjects and patients in shock Circulation 31 523 1965
4 Dietzman R H Castaneda A R Lillehei C W Ersek R A Motsay G J and Lillehei C Corticosteroids as effective vasodilators in the treatment of low output syndrome Chest 5 440 1970
5 deMello V R Roberts R and Sobel B E Deleterious effects of methylprednisolone in patients with evolving myocardial infarction Clin Res 33 179 1975
6 Vyden J K Tomoda, H Prakash R Chuck L Parmley W W and Corday E Effect of corticosteroids in shock secondary to myocardial infarction Circulation 44 II 237 1971
7 Valori C Thomas M and Shillingford J Free noradrenaline and adrenaline excretion in relation to clinical syndromes following myocardial infarction Am J Cardiol 20 605 1967
8 Raab W Cardiovascular effects of desoxycorticosterone acetate in man AM HEART J 24 365 1942
9 Kurland G S and Freedberg H S Potentiating effects of ACTH and cortisone on pressor response to intravenous infusion of l norepinephrine Proc Soc Exp Biol Med 78 28 1951
10 Spink W W The pathogenesis and management of shock due to infection Arch Intern Med 106 433 1970
11 Dustan H Corcoran A C Taylor R D and Page I H Cortisone and ACTH in essential hypertension establishment of renal glycosuria Arch Intern Med 87 627 1950
12 Sambhi M P Weil M H and Udhoji V N Pressor responses to norepinephrine in humans before and after corticoids Am J Physiol 203 961 1962
13 Chapman D W Skaggs R H Thomas J R and Greene J A The effect of cortisone in experimental myocardial infarction Am J Med Sci 223 41 1952
14 Johnson A S Scheinberg S R Gerisch R A and Saltzstein H C The effect of cortisone on the size of experimentally produced myocardial infarcts Circulation 7 224 1953
15 Opdyke D F Lambert A Stoerk H C Zanetti M E and Kuna S Failure to reduce the size of experimentally produced myocardial infarcts by cortisone treatment Circulation 8 544 1953
16 Hepper N G Pruitt R D Donald D E and Edwards J E The effect of cortisone on experimentally produced infarcts Circulation 11 742 1955
17 Dall J L C and Peel A A F A trial of hydrocortisone in acute myocardial infarction Lancet 2 1097 1963
18 Barzilai D Plavnick J Hazani A Einath R Kleinhaus N and Kanter Y Use of hydrocortisone in the treatment of myocardial infarction Chest 61 488 1972
19 Scientific subcommittee of the Scottish Society of Physicians Hydrocortisone in severe myocardial infarction Lancet 2 785 1964
20 Libby P Maroko P R Bloor C M Sobel B E and Braunwald E Reduction of experimental myocardial infarct size by corticosteroid administration J Clin Invest 52 599 1973

Table II Non-riboflavin deficient patients

Case No	Age	Diagnosis	CHF	Percentile Wt	Percentile Ht	Heart size (ECG x ray)	Second diagnosis	Drugs	Hb (Gm./dl)	EG RAC
?1	1 mo	Con enital heart disease trans position of great vessels	0	< 10	90	Right ventricu lar hypertro phy lar e	–	Digoxin penicillin	14 8	1 0
??	2 mo	Congenital heart disease tricus pid atresia	0	?5	25	Left ventricular hypertrophy normal	–	–	15 3	1 0
16	? mo	Congenital heart disease tricus pid atresia	0	3	10	Left ventricular hypertrophy normal	–	–	1? 4	1 0
3	1 yr	Congenital heart disease tricus-pid atresia	0	> 10	> 25	Left ventricular hypertrophy normal	–	–	16 5	1 0
14	1 yr	Congenital heart disease tetral ogy of Fallot	0	3	10	Left ventricular hypertrophy normal	–	–	1? 4	1 0
1	1 yr	Congenital heart disease ven tricular septal defect persist ent ductus ar terio u	+	?0	25	Left ventricular hypertrophy large	–	–	12 4	1 0
?3	1 yr	Congenital heart disease ven tricular septal defect	+	3	10	Biventricular hypertrophy large	–	Digoxin	12 0	1 0
10	2 yr	Congenital heart disease ven tricular septal defect atrial septal defect	+	10	25	Right ventricu lar hypertro phy normal	–	–	12.2	0 ?
?0	? yr	Congenital heart disease pa tent ductus arteriosus	0	50	25	Upper limits of normal nor mal	–	–	13 6	1 0
18	? yr	Congenital heart disease tetral ogy of Fallot	0	3	?5	Right ventricu lar hypertro phy normal	–	–	17 4	1 0
13	2 ? yr	Congenital heart disease ven tricular septal defect aortic insuffi	0	10	?5	Left ventricular hypertrophy normal	–	–	12 4	1 0
11	? yr	Congenital heart disease ven tricular septal defect atrial septal defect pulmonary valvular ste nosis	0	3	?5	Right ventricu lar hypertro phy normal	–	–	14 0	0 9
?	3 yr	Congenital heart disease tetral ogy of Fallot	0	??	25	Right ventricu lar hypertro-phy normal	–	–	1? 2	1 0

EGRAC erythrocyte glutathione reductase activity coefficient [illegible]

Table I Riboflavin deficient patients

Case No	Age (yr)	Diagnosis	CHF	Percentile		Heart size (ECG x ray)	Second diagnosis	Drugs	Hb (Gm/dl)	EGRAC
				Wt	Ht					
15	1/2	Congenital heart disease ventricular septal defect	+	10	25	Left ventricular hypertrophy large	Pneumonia	Penicillin digoxin chlorothiazide	11 3	16
11	1	Congenital heart disease ventricular septal defect	+	> 10	25	Left ventricular hypertrophy large	Pneumonia	Penicillin digoxin	10 8	1 5
12	1	Congenital heart disease tricuspid atresia	0	3	3	Left ventricular hypertrophy normal	–	–	17 8	1 4
19	2½	Congenital heart disease tetralogy of Fallot	0	10	25	Right ventricular hypertrophy normal	–	–	16 8	1 3
2	3	Congenital heart disease tetralogy of Fallot	0	> 3	> 10	Right ventricular hypertrophy normal	–	–	17 3	1 5
4	3	Congenital heart disease ventricular septal defect	+	> 3	3	Biventricular hypertrophy large	Pneumonia	Penicillin digoxin	11 5	1 57
8	5	Congenital heart disease ventricular septal defect	+	> 50	> 25	Biventricular hypertrophy large	Pneumonia	Penicillin digoxin chlorothiazide	9 8	1 43
31	10	Rheumatic heart disease mitral insuffic + myocarditis	+	75	50	Left ventricular hypertrophy large	–	–	14 2	1 5
25	12	Congenital heart disease ventricular septal defect aortic insuffic	0	25	50	Normal normal	–	–	12 5	1 3
1	13	Rheumatic heart disease mitral insuffic + myocarditis	+	> 50	> 25	Left ventricular hypertrophy large	–	Penicillin prednisone digoxin	13 0	1 39
7	13	Rheumatic heart disease mitral insuffic + myocarditis	+	50	75	Left ventricular hypertrophy large	Asthma	Penicillin prednisone digoxin KCl	12 0	1 38

EGRAC erythrocyte glutathione reductase activity coefficient

insufficiency and myocarditis Seven of the 11 were in congestive heart failure (CHF) when these studies were performed

Of the 20 with no evidence of riboflavin deficiency, 19 had congenital disease and one had rheumatic heart disease Only four were in congestive heart failure (Table II)

Socioeconomic factors All the infants and children in this study were from the same socioeconomic level and no gross dietary differences could be discerned between the groups

Seven of the 11 riboflavin deficient patients were below the fiftieth percentile for weight and eight were below the fiftieth percentile for height In comparison 10 of the 20 without riboflavin deficiency were below the fiftieth percentile for

deficiency and duration of the heart disease the deficiency occurring in both the younger and older children

There ■ no *reason to believe* that the nutritional deficiencies in children with cardiac disease are limited to that of folic acid and riboflavin. The *latter* have *been* studied since specific and quantitative methods are available for these purposes. It is probable however that these children may be subject to multiple nutritional deficiencies which are the result of poor appetite, malabsorption in those with congestive heart failure and possibly other factors presently not known. The B vitamins are concerned with tissue respiration and deficiencies may *affect not only* heart tissue metabolism but the general well being of the child. It is therefore important to insure that each child with *cardiac disease* receives an adequate intake of essential nutrients and that he be checked periodically for nutritional deficiencies.

Summary

Thirty one infants and children with cardiac disease were randomly selected to determine whether riboflavin deficiency is more prevalent among those with cardiac disease than among a group of comparable socioeconomic status without cardiac disease. Riboflavin studies were initiated since it is a representative *member of the* B complex and a specific and sensitive biochemical *method* ■ available to detect deficiency of this vitamin. The method involves the determination of the degree *of saturation of erythrocyte* glutathione reductase. Twenty seven of the subjects had congenital heart disease and *four* had rheumatic heart disease. Eleven of the 31 had evidence of riboflavin deficiency, a significantly higher prevalence than among the group without cardiac disease. The *deficiency existed among* those with congenital and acquired cardiac disease. There was a greater tendency for the *vitamin deficiency to occur among those with* congestive heart failure. These studies indicate that nutritional deficiencies may be more prevalent *among infants* and children with cardiac disease than was previously thought.

REFERENCES

1. Grasbeck, R, Bjorksten, F, and Nyberg, W: Formimino- [illegible] Nord. Med. 66 1343 1961
2. Daly, J J, and Rose, D P: Excretion of urocanic acid following oral histidine in heart failure. Br Heart J 28 698 1966
3. Brody, J I, Soltys, H D, and Zinsser, H F: Folic acid deficiency in congestive heart failure. Br Heart J 31 741 1969
4. Rook, G D., Lopez, R, Shimizu, N., and *Cooperman*, J M: Folic acid deficiency in infants and *children with* heart disease. Br Heart J 35 87 1973
5. Hyde, R D, and Loehry, C A E ■: *Folic* acid malabsorption in cardiac failure. Gut 9 ‹17 1968
6. Retief, F P, and Huskisson, J J: *Serum* and urinary folate in liver disease. Br Med. J 2 *150 1969*
7. Glatzle, D, Korner, W F., Christeller, S., and Wiss, O: Method for the detection *of a biochemical* riboflavin deficiency. Int J Vitamin Res *40 166 19 0*
8. Cooperman, J M, Cole, H S, *Gordon*, M, and Lopez, R: Erythrocyte glutathione *reductase as* a measure of riboflavin nutritional *status of* pregnant women and newborns. Proc Soc *Exp Biol Med* 143 *376* 19 3
9. Cole, H S, Lopez, R., and Cooperman, J M: Quantitative estimation of riboflavin *deficiency* in a low socio-economic pediatric *population by a new method*. Pediatr Res ■ 379 19 4
10. Tillotson, J A., and Sauberlich, H ■: Effect of riboflavin depletion and *repletion on* the erythrocyte glutathione reductase in the rat. J Nutr 101 1459 1971
11. Tillotson, J A, and Baker, E M: An enzymatic measurement of the riboflavin *status* in man. Am J Clin Nutr 25 425 1972

Table II cont d

Case No	Age	Diagnosis	CHF	Percentile		Heart size (ECG x ray)	Second diagnosis	Drugs	Hb (Gm./dl)	EG RAC*
				Wt	Ht					
28	4 yr	Congenital heart disease tetralogy of Fallot	0	10	10	Right ventricular hypertrophy normal	Pectus excavatum	–	14 7	10
20	5 yr	Congenital heart disease tetralogy of Fallot	+†	10	3	Right ventricular hypertrophy normal	–	Digoxin chlorothiazide	14 7	10
24	5 yr	Congenital heart disease tetralogy of Fallot	0	10	25	Right ventricular hypertrophy normal	–	–	17 5	10
27	8 yr	Congenital heart disease atrial septal defect	0	50	25	Right ventricular hypertrophy large	–	–	12 6	10
5	10 yr	Rheumatic heart disease mitral insuffic + stenosis	0	25	> 25	Left atrial and left ventricular hypertrophy large	–	Penicillin	13 0	10
29	11 yr	Congenital heart disease coarctation of the aorta ventricular septal defect	0	25	50	Left ventricular hypertrophy normal	–	–	14 0	10
[illegible]	18 yr	Congenital heart disease ventricular septal defect	0	50	50	Right ventricular hypertrophy normal	–	–	18 0	11[illegible]

weight and 18 below the fiftieth percentile for height There were no significant differences between the two groups at the third and fiftieth percentiles for height and weight

Discussion

The estimation of erythrocyte glutathione reductase permits, for the first time a specific and sensitive means to determine riboflavin deficiency Studies with experimental riboflavin deficiency in the rat[10] and in the human being[1] demonstrated that an increase in AC values was an early and specific indicator of riboflavin deficiency and that this increase correlated well with the duration and severity of the deficiency In both species the AC values returned to within normal range after repletion with riboflavin It was subsequently shown that this method is applicable to infants and children [8]

The prevalence of riboflavin deficiency as determined by the biochemical test was significantly greater among the children with cardiac disease than among a group of children of the same socioeconomic level without heart disease

Growth and development There were no differences in height and weight between the children with heart disease with and without riboflavin deficiency As a group however the children with cardiac disease were smaller and weighed less than normal children of the same socioeconomic status and ethnic background Only eight of the 31 study subjects were at the fiftieth percentile or higher for weight and height It is apparent that the retardation of growth was not solely attributable to riboflavin deficiency

Cardiac disease The heart lesions in both the riboflavin deficient and non-riboflavin deficient groups were similar, however there was a greater occurrence of congestive heart failure among the deficient children This may have contributed to the vitamin deficiency since these seriously ill children probably had a poorer dietary intake combined with gastrointestinal malabsorption which often accompanies congestive heart failure

There was no correlation between riboflavin

Table I Criteria for the presence of digoxin intoxication

Electrocardiographically documented sinus rhythm in all the patients before administration of digoxin and complete resolution of any of the arrhythmias given below with discontinuation of digoxin including treated patients
A Ectopic ventricular rhythm
Multifocal ventricular ectopic beats
Unifocal ventricular ectopic beats more than 5 per minute
Ventricular bigeminy or trigeminy or tachycardia
B Nonparoxysmal atrioventricular (A V) tachycardia
A V junctional escape rhythm and A V junctional exit block
C A V dissociation with ventricular rate exceeding atrial rate
D Atrial fibrillation with ventricular response less than 60 per minute if accompanied by ectopic ventricular beats
E Sinus rhythm with second or third degree A V block
F Paroxysmal atrial tachycardia with A V block

Serum magnesium The mean serum magnesium concentration in 19 children receiving digoxin and diuretics was lower than in 18 healthy control subjects The magnesium levels were further lowered when mean values in toxic and hypomagnesemic patients were compared with those in healthy control subjects (Table IV) Magnesium deficiency (less than 1 5 mEq per liter) was encountered in five out of nine toxic patients and in three out of 10 nontoxic subjects

Serum digoxin and dosage The mean serum digoxin level in 10 nontoxic children was 2 24 ± 0 46 (1 5 to 2 8) ng per milliliter and in nine toxic ones it was 4 4 ± 2 51 (1 3 to 10 1) ng per milliliter The difference was statistically significant ($P < 0.05$) but there was no significant difference in dosage schedules between the two groups

Other laboratory data Mean concentrations of other laboratory data did not show much abnormality (Table III) Serum sodium and chloride were slightly lowered Mean blood urea was significantly higher ($P < 0.05$) in the toxic group (40 6 ± 15.3 mg per 100 ml) as compared to nontoxic patients (28 7 ± 7 0 mg per 100 ml) and this may be the cause of higher digoxin levels in toxic patients.

Management Potassium chloride orally and magnesium sulfate intravenously were used for the management of digoxin toxicity

Table II Clinical data in 19 children receiving digoxin and diuretics

Datum	*No*	*Per cent*
Age 10 years and less	7	36 8
Sex male	14	73 6
Class III and IV heart failure	10	52 6
Other medications		
Furosemide	13	68 4
Prednisolone	4	21 0
Potassium chloride	13	68 4
Etiological diagnosis		
Rheumatic heart disease	[illegible]	84.2
Congenital heart disease	2	10 5
Cardiomyopathy	1	5 2
Risk factors		
Subacute bacterial endocarditis	1	5 2
Acute rheumatic carditis	5	26 3
Sinus rhythm	19	100 0
Toxic manifestations (9 cases)		
Extracardiac	7	36.8
Cardiac		
Ventricular bigeminy or trigeminy	3	15 7
Multifocal ventricular ectopic beats	2	10.5
Second-degree (Mobitz type II) A V–block	4	21.5
Deaths	–	–

Table III Laboratory data in 19 children receiving digoxin

Datum	*Normal*	*Mean ± S D (range)*	
Blood urea (mg /100 ml)	0-40	34 3 ± 12 9	(18-[illegible])
Serum creatinine (mg /100 ml)	0 6 1 2	1 03 ± 0 17	(0 8-1 5)
Serum sodium (mEq /L.)	1[illegible]0 135	123 ± 6 4	(112 133)
Serum potassium (mEq /L.)	3 5-5 0	4 0 ± 0.39	(3.5-4 8)
Serum chloride (mEq/L.)	85 110	90 8 ± 5 6	(80-102)
Serum calcium (mg /100 ml)	9 0 11 0	9 [illegible] ± 0 41	(9 0-10 4)

Digoxin and diuretics were stopped in all the patients as soon as toxicity was detected No specific antiarrhythmic drug was given to patients with Mobitz type II A V block In three patients who had hypomagnesemia 10 to 20 ml of 20 per cent magnesium sulfate was administered slowly intravenously in 10 to 25 minutes In two cases arrhythmias disappeared within 15 minutes and in one after 30 minutes of infusion of magnesium sulfate (Table V) In two patients who had

Hypomagnesemia in relation to digoxin intoxication in children

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Recently an increased prevalence of hypomagnesemia has been demonstrated in patients treated with digitalis and diuretics[1-4] Hypomagnesemia decreases intracellular myocardial potassium content and sensitizes it to the effects of digoxin However low serum magnesium level directly may also be responsible for the increased risk of digoxin intoxication among these patients Therefore magnesium sulfate may be used for the management of digoxin toxicity in patients associated with hypomagnesemia

These observations made in experimental animals and adult patients prompt us to re evaluate the serum magnesium concentrations in children treated with digoxin and diuretics

Material and methods

This prospective study was conducted in the Medical Wards of the University Hospital Varanasi India from January 1972 to June 1973 Only those 19 children were included in this study who were receiving Lanoxin brand of digoxin (Burroughs Wellcome and Company)

Serum magnesium estimation was done by the method of Andreason after at least 1 week of digitalization and diuretic therapy Patients with rheumatic heart disease (16 cases) were on prolonged therapy with digoxin and diuretics Serum magnesium values were obtained in 18 healthy children for controls

Serum digoxin estimation was done by radioimmunoassay[6] Other laboratory data e g blood urea serum creatinine sodium potassium chloride and calcium, were obtained by standard methods Clinical radiological electrocardiographic and other necessary data were obtained to determine the cause and nature of heart failure The criteria for the presence of digoxin intoxication were similar to those found by other investigators[1] (Table I)

Student's t test was employed for the analysis of data

Observations

Out of 19 children ranging between 2 and 16 years age and weighing between 10 and 44 kilograms 10 nontoxic ones (mean age 10 1 ± 4 74 years, mean body weight 24 5 ± 10 0 kilograms) were receiving 0 4 ± 0 27 (0 125 to 0 75) mg per day of mean digoxin and the nine toxic ones (mean age 12 1 ± 3 75 years, mean body weight, 28 7 ± 8 9 kilograms) were receiving 0 47 ± 0 25 (0 125 to 0 75) mg per day of mean digoxin and 40 to 80 mg per day of furosemide for control of heart failure Most of the patients were receiving prophylactic potassium chloride in a dosage of 15 grains three times a day (Table II) Clinical data were similar in both nontoxic and toxic patients

Degree duration and manifestations of digoxin intoxication Table II shows the degree of digoxin toxicity in the form of electrocardiographically documented rhythm disturbances in nine toxic patients Seven of them were associated with noncardiac symptoms of digoxin intoxication The serum digoxin level in each individual patient was more than 2 5 ng per milliliter excluding one patient with Mobitz type II A V block (Table V) The duration of digoxin toxicity in all the patients before therapy was 4 to 6 hours

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cardium to digitalis increases its uptake and induces digoxin toxicity with doses which are ordinarily nontoxic[1] The cause of magnesium deficiency among these patients is possibly increased diuresis and magnesuria[2]

In three patients who had magnesium deficiency arrhythmias disappeared with magnesium sulfate therapy (Table V) It is likely that magnesium administration resulted in a rapid decrease in arterial potassium concentration indicating that there is a cellular uptake of potassium This effect of magnesium sulfate may be one of those overcoming the ATPase inhibition induced by digitalis because when it is administered alone it does not cause an influx of myocardial potassium[7]

At the end it should be noted that hypomagnesemia is very common in children receiving digoxin and diuretics and that patients with magnesium deficiency are predisposed to a higher risk of digoxin toxicity Magnesium replacement may be preferred among these patients for the management of digoxin induced cardiac arrhythmias

Summary

Serum magnesium estimation was done in 19 children who had heart failure of varied etiology Five of nine toxic patients and three of 10 non toxic ones had magnesium deficiency (serum magnesium < 1.5 mEq per liter) Mean serum magnesium level was significantly lowered ($P < 0.01$) in 19 children and it was further lowered in nine toxic patients ($P < 0.001$) as well as in eight hypomagnesemic patients ($P < 0.001$) than in healthy control subjects Mean serum digoxin level in toxic patients was significantly higher than in nontoxic ones ($P < 0.05$) In three cases magnesium sulfate was successfully used for the management of cardiac arrhythmias

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REFERENCES

1 Seller R H Ramirez O Brest A N and Moyer J H Serum and erythrocyte magnesium levels in congestive heart failure Am J Cardiol 17 786 1966
2 Jackson, C E, and Meir D W Routine serum magnesium analysis Ann Intern Med 69 43 1968
3 Lim P and Jacob P Magnesium deficiency in patients on long term diuretic therapy for heart failure Br Med J 3 620 1972
4 Singh, R B Srivastav D K Dube S S Dube K P and Vaiş, S K Hypomagnesemia and digoxin therapy J Assoc Phys India 22 427 1974
5 Beller G A Hood W B Jr Smith T W Abelmann W H, and Wacher W E Prevalence of hypomagnesemia in a prospective clinical study of digitalis intoxication Am J Cardiol 26 625 1970
6 Seller R H Casiano J Kim K E Mendelsshon S Brest A N and Swartz C Digitalis toxicity and hypomagnesemia, Am Heart J 79 57 1970
7 Neff M S Saul M Kim K E Banach S Swartz C and Seller R H Magnesium sulphate in digitalis toxicity Am J Cardiol 29 377 1972
8 Andersson, E On the determination of magnesium in the serum and urine by titan yellow method Scand Clin Lab Invest 9 138 1957
9 Smith T W Butler V P Jr and Haber E Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay N Engl J Med 281 1212 1969
10 Beller G A, Smith T W Abelmann W H Haber E and Hood, W E Digitalis intoxication clinical correlations with serum levels, N Engl J Med 284 989 1971
11 Singh R B Vaiş S K Rai A N and Dube K P Risk factors of digoxin intoxication J Indian Med Assoc 64 36 1975
12 Neill C A The use of digitalis in infants and children Prog Cardiovasc Dis 7 399 1965
13 Seller R H The role of magnesium in digitalis toxicity Am Heart J 82 551 1971
14 Johnston C L Pinkus N B and Down M Plasma digoxin levels in digitalised and toxic patients Med J Aust 1 863 1972
15 Singh, R B Rai, A N Dube K P Somani, P N and Katiyar B C Radioimmunoassay of serum digoxin levels in relations to digoxin intoxication Br Heart J 37 619 1975
16 Dunham E T and Glynn I M Adenosine triphosphatase activity and the active movements of the alkali metal ions J Physiol (Lond) 156 274 1961
17 Lown B and Levine S A Current concepts in digitalis therapy N Engl J Med 250 771 1954
18 Harrison C E, Jr, and Brown A L Jr Myocardial digoxin H content in experimental hypokalaemic cardiomyopathy J Lab Clin Med 72 118 1968
19 Prindle K H Skeleton C L Epstein S E and Marcus F I Influence of extracellular potassium concentration on myocardial uptake ionotropic effect of triated digoxin Circ Res 28 337 1971
20 Hannah, S Harrison M Macintyre J and Frager R Syndrome of magnesium deficiency in man Lancet 2 172, 1960

Table IV Serum magnesium levels in different groups of patients in relation to healthy controls

	Healthy controls	Various groups		
		Total	*Toxic*	*Hypo magnesemic*
Number	18	19	9	8
Mean ± S D (ng/ml)	1 76 ± 0 13	1 58 ± 0 24	1 [illegible] ± 0 20	1 36 ± 0 0[illegible]
Range	1 5 2 1	1 3 2 1	1 3 1 8	1 3 1 4
P value	–	< 0 01	< 0 001	< 0 001

no magnesium deficiency potassium chloride orally in double the dosage (30 grams thrice daily) was continued Much more time was required by these patients than by magnesium treated ones for the disappearance of cardiac arrhythmias (Table V)

Discussion

It is known that dosages of digitalis and therapeutic serum digoxin concentrations vary from patient to patient They may also vary from time to time in the same patient the cause being electrolyte disturbances metabolic alterations drugs hormones and autonomic influences which may influence the uptake of digoxin and may render the myocardium more sensitive to the effects of drug[11] To the contrary some patients (e g children) tolerate a relatively higher digoxin concentration as compared to adults However this property of children s myocardium may be lost in the presence of hypokalemia and hypomagnesemia sensitizing it to the toxic effects of digoxin [11] Similarly renal insufficiency as a risk of toxicity has been observed by many investigators[1, 14] The dosage of digoxin should be reduced because the drug is not excreted It is interesting to note that the mean serum digoxin concentration in toxic patients of this study was significantly higher than in nontoxic ones but there was no significant difference in the mean dosage of digoxin between the two groups The cause may be that renal functions in the toxic patients were impaired (mean blood urea 40 6 ± 15 3 mg per 100 ml)

Hypokalemia was not found in our patients as most of them were receiving prophylactic potassium chloride along with diuretics However

Table V Results of treatment in toxic patients

No rhythm	Serum level			Treatment	Duration of therapeutic response
	Dig (ng / ml)	K (mEq /L)	Mg (mEq /L)		
1 Bigeminy	2 6	4 6	1 3	Magnesium sulfate	15 min
2 Bigeminy	3 2	4 8	1 3	Magnesium sulfate	10 min
3 Trigeminy	3 9	3 8	1 7	Potassium chloride	8 hr
4 Multifocal ectopic beats	3 0	4 2	1 4	Magnesium sulfate	[illegible]0 min
5 Multifocal ectopic beats	10 1	3 8	1 8	Potassium chloride	1[illegible] hr
6 Mobitz type II A V block	1 1	3 9	1 4	No specific treatment	24 hr
7 Mobitz type II A V block	4 8	4 0	1 7	No specific treatment	8 hr
8 Mobitz type II A V block	4 9	4 0	1 6	No specific treatment	1[illegible] hr
9 Mobitz type II A V block	3 2	4 2	1 3	No specific treatment	10 hr

magnesium deficiency was quite frequent (eight out of 19 children) Mean serum magnesium concentration was significantly lowered (P < 0 01) in 19 children and it was further diminished in toxic patients (nine cases) as well as in hypomagnesemic patients (eight cases) than healthy controls (Table IV) Five of nine toxic patients had frank hypomagnesemia (serum magnesium < 1 5 mEq per liter) These observations confirm the previously held view that hypomagnesemia is highly prevalent in adult patients treated with digoxin and diuretics and also in those who had digoxin toxicity It is likely that magnesium deficiency has predisposed these patients to digoxin intoxication

The mechanism could be that digitalis inhibits cell membrane adenosine triphosphatase (ATPase) activity resulting in decreased intracellular potassium and magnesium is a metallo coenzyme that activates ATPase[1] It is likely that magnesium deficiency contributes digitalis induced ATPase blockade resulting in a greater loss of intracellular potassium and sensitizes the myo

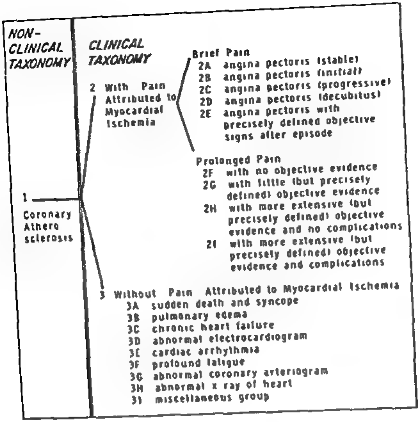

Fig 1 Spectrum of coronary atherosclerotic heart disease—clinical taxonomy

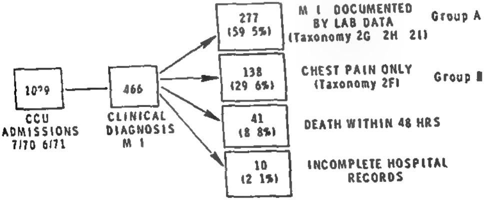

Fig 2 Categorization of patients Coronary-care unit admissions July 1970 through June 1971

only during the final 2 months of this study

A 2 by 2 chi square determination was used to compare the patients with a typical history of myocardial infarction *with* and *without* laboratory documentation differences were considered significant when $p < 0.05$

Results

Fig 2 shows the 466 myocardial infarction patients admitted to the CCU between July 1970 and June 1971 Included are 277 patients (Group A) with myocardial infarction documented by laboratory data (clinical taxonomy 2G 2H 2I) 138 patients (Group B) with chest pain only (clinical taxonomy 2F) and 41 patients excluded from the study because of death within the first 48 hours Ten patients were not categorized because of incomplete hospital records

The one year prognosis of patients in Group A (documented myocardial infarction group—clin

Myocardial infarction with and without laboratory documentation—one year prognosis

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The patient with chest pain typical for myocardial infarction admitted to a coronary care unit (CCU) who has no objective (laboratory) documentation of myocardial infarction presents the clinician with a management dilemma This is particularly so when the history of chest pain causes the physician to treat the patient as if myocardial infarction had occurred The group of patients with chest pain only is of increasing interest because the prognosis of these patients the determinant of long term management is unknown

This retrospective study was designed to compare the in hospital mortality rate the one year mortality rate and the incidence of recurrent myocardial infarction in patients with chest pain suggestive of myocardial infarction and admitted to a CCU who developed or failed to develop confirmatory laboratory data

Acute coronary insufficiency preinfarction syndrome, preinfarctional (unstable) angina and noninfarction cases are among the terms used to describe some of the prolonged pain syndromes associated with coronary atherosclerotic heart disease Hurst has described a clinical taxonomy (Fig 1) that delimits these syndromes by clinical criteria this taxonomy will be used to describe the subgroups in this study

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Study design

Hospital records were available for review for 1 029 of the 1 039 patients admitted to the Grady Memorial Hospital coronary care units for the year July 1 1970 through June 30 1971 A total of 466 of these patients were admitted with a clinical diagnosis of myocardial infarction These 466 patients were subdivided into two groups Group A consisted of patients with laboratory documentation of myocardial infarction including the appearance of Q waves on the electrocardiogram (ECG) (clinical taxonomy 2H and 2I) Also included in this group were patients with serial ST and/or T wave changes consistent with myocardial ischemia or elevated serum enzyme levels including creatine phosphokinase lactic dehydrogenase isoenzymes and glutamic oxal acetic transaminase (clinical taxonomy 2G) Group B included patients with chest pain typical for myocardial infarction but *without* laboratory documentation (clinical taxonomy 2F) The 41 patients who died within 48 hours after admission were excluded from analysis because of the lack of availability of the laboratory data needed to accurately group them The 14 patients with incomplete one year follow up were considered separately

Because this was a retrospective study there was no predetermined protocol for ordering ECG s or serum enzyme determinations However all patients admitted to the CCU had at minimum a 12 lead ECG on days 1 2 and 3 Most patients with chest pain only (clinical taxonomy 2F) had one to five serum enzyme determinations but the creatine phosphokinase was available

tion. One patient in *Group B* died during coronary artery bypass surgery

Six of the 55 deaths in *Group A occurred* outside the hospital and *were definitely noncardiac* Reasons for death included automobile accidents (1) carcinoma of the colon (1) cerebrovascular accident (1) pulmonary embolus (1) carcinoma of the bladder (1) and renal failure (1)

Deaths (of unknown cause) outside the hospital occurred in 28 of 55 (51 per cent) patients in *Group A and in 10 of 18 (55 per cent)* in Group B This difference is not significant Three patients in Group A had had *an interim hospitalization for* recurrent myocardial infarction

The incidence of recurrent myocardial infarction was comparable for the documented myocar*dial infarction (Group A)* and *chest* pain only (Group B) groups 10 2 and 9 9 per cent respectively (Table IV)

Comment

The prognosis has been *previously reported for* patients *in the* clinical subgroups of prolonged pain with little (but precisely defined) objective evidence (clinical taxonomy 2G) prolonged *pain with more extensive (but precisely defined)* evidence and no complications (clinical taxonomy 2H) and *prolonged pain with more* extensive *(but precisely defined) objective evidence* and complications (clinical taxonomy 2I) The prognosis was *not previously* reported for patients with clinical taxonomy 2F—prolonged pain but no objective evidence

Summary

This retrospective study indicates that patients admitted to our CCU with a history *typical for* myocardial infarction *appear to* have a comparable in hospital mortality *rate after 48 hours* a *comparable* one year mortality rate and a comparable incidence of *recurrent myocardial* infarction *during the first* year whether or not they develop confirmatory ECG or serum enzyme changes Patients with chest pain typical of myocardial infarction who fail to develop confirmatory ECG *or serum enzyme* changes, would appear to require the same care and follow up as do those patients admitted with chest pain who *do develop such ECG or serum* enzyme changes

The authors wish to acknowledge the assistance of Ms Betty Atwood and Julia Wright in the preparation of this manuscript

REFERENCES

1 Hurst, J W The heart ed 3 New York 1974 McGraw Hill Book Company Inc., p 1039
2 Weinblatt E Shapiro S Frank C W and Sager R V Prognosis of men after first myocardial infarction *Mortality* and first recurrence in relation to selected parameters Am J Pub Health 58 1329 1968
3 Murnaghan D Hickey N and Mulcahy R Immediate and long term experience of acute coronary insufficiency abstracted Br Heart J 32 565 1970
4 Vakil R M Pre-infarction syndrome Management and follow up Am J Cardiol 14 55 1964
5 Lopes M F Spivak A P Harrison [illegible] C and Schroeder J S Prognosis in coronary care unit noninfarction cases J A M A 228 1558 1974
6 Krauss K R Hutter A M and DeSanctis R W Acute coronary insufficiency Course and follow up Arch Intern Med 129 808 1972
7 Kannel W B and Feinleib M atural history of angina pectoris in the Framingham Study Prognosis and survival Am J Cardiol 29 154 1972
8 Norris R M Caughey D E Mercer C J and Scott P J Prognosis after myocardial infarction Br Heart J 36 786 1974
9 Norris R M Caughey D E Mercer C J Deeming L W and Scott P J Coronary prognostic index for predicting survival after recovery from acute myocardial infarction Lancet 2 485 19[illegible]
10 Thygesen K Dalsgaard P and Nielsen B L Prognosis after first myocardial infarction Acta Med Scand 195 [illegible]3 19[illegible]4
11 Gazes, P C Mobley E M Faris H M Duncan R C., and Humphries G B Preinfarctional (unstable) angina—A prospective study—Ten year follow up *Circulation* 48 331 1973
12 Sigler L H Prognosis of angina pectoris and myocardial infarction Further report Am J Cardiol 6 [illegible]52 *1960*
13 Sigler L H Prognosis of angina pectoris and *coronary* occlusion Follow-up of 1 [illegible]00 cases J A M A 146 *998* 1951
14 Fulton M Duncan B Lutz W., Donald K W., Kirby B J Morrison S L., Kerr F Julian D G., and Oliver M F Natural history of unstable angina Lancet 1 *860* 1972

Table I One year prognosis Documented myocardial infarction and chest pain only groups

Status	Group A documented MI (taxonomy 2G 2H 2I) n = 277	Group B chest pain only (taxonomy 2F) n = 138
Alive	215 (77 6%)	113 (81 9%)
Deceased	55 (19 9%)	18 (13 0%)
Incomplete follow up	7 (2 5%)	7 (5 1%)

Table II Deaths with and without prior myocardial infarction Documented myocardial infarction and chest pain only groups

	Group A documented MI (taxonomy 2G 2H 2I)	Group B chest pain only (taxonomy 2F)
History prior MI	n = 97 21 (22%)	n = 60 10 (17%)
No history prior MI	n = 173 34 (20%)	n = 71 8 (11%)

ical taxonomy 2G, 2H, 2I) and that of Group B (chest pain only—clinical taxonomy 2F) are compared in Table I They are not statistically different ($p > 0\,10$) The one year mortality rates were 19 9 and 13 0 per cent for the documented myocardial infarction group (clinical taxonomy 2G 2H 2I) and the chest pain only group (clinical taxonomy 2F) respectively

These two patient groups were next analyzed according to the history of prior myocardial infarction Ninety seven (36 per cent) of Group A (270 patients) and 60 (46 per cent) of 131 patients in Group B had history of prior myocardial infarction ($p > 1\,0$) This appeared important inasmuch as ECG changes of prior myocardial infarction might limit the diagnostic ECG data available with a recurrent myocardial infarction

Table II shows that there was no significant difference in one year mortality rate *with* or *without* prior myocardial infarction in either Group A or Group B The one year mortality rate was 22 per cent (21 patients) for the 97 patients in Group A with a documented myocardial infarc

Table III Deaths during the one year follow up Documented myocardial infarction and chest pain only groups

	Group A documented MI (taxonomy 2G 2H 2I) n = 55	Group B chest pain only (taxonomy 2F) n = 18
DIED index hospitalization	20 (36%)	4 (22%)
DIED hospitalization for recurrent MI	1 (2%)	3 (17%)
DIED coronary bypass surgery		1 (6%)
Noncardiac death	6 (11%)	
Death outside hospital unknown cause	28 (51%)	10 (55%)
(Interim hospitalization for MI)	(3)	

Table IV Recurrent myocardial infarction Documented myocardial infarction and chest pain only groups

Group A documented MI (taxonomy 2G 2H 2I) n = 270	Group B chest pain only (taxonomy 2F) n = 131
28 (10 2%)	13 (9 9%)

tion, and 17 per cent (10 patients) for the 60 patients in Group B who had prior myocardial infarction The one year mortality rate was 34 of 173 (20 per cent) for patients in Group A and eight of 71 (10 per cent) for patients in Group B who had no history of prior myocardial infarction

The 55 deaths in Group A and the 18 deaths in Group B during the one year follow up are further analyzed in Table III the numbers of deaths in most of the subgroups were too small for meaningful comparison

Twenty of 55 deaths (36 per cent) in the Group A patients with documented myocardial infarction and four of 18 (22 per cent) of the chest pain only patient deaths occurred during the index hospitalization after 48 hours One death (2 per cent) in Group A and three of the 18 deaths (17 per cent) in Group B occurred during a subsequent hospital admission for myocardial infarc

tion One patient in Group B died during *coronary artery bypass surgery*

Six of the 55 deaths in Group A occurred outside the hospital and *were definitely noncardiac* Reasons for death included automobile accidents (1) carcinoma of the colon (1) cerebrovascular accident (1) pulmonary embolus (1) carcinoma of the bladder (1) and renal failure (1)

*Deaths (of unknown cause) outside the hospi*tal occurred in 28 of 55 (51 per cent) patients in Group A and in 10 of 18 (55 per cent) in Group B This difference is not significant Three patients in Group A had had an interim hospitalization for recurrent myocardial infarction

The incidence of recurrent myocardial infarction was comparable for the documented myocardial infarction (Group A) and chest pain only (Group B) groups 10 2 and 9 9 per cent respectively (Table IV)

Comment

The prognosis has been previously reported for patients in the clinical subgroups of prolonged pain with little (but precisely defined) objective evidence (clinical taxonomy 2G) prolonged pain with more extensive (but precisely defined) evidence and no complications (clinical taxonomy 2H) and prolonged pain with more extensive (but precisely defined) objective evidence and complications (clinical taxonomy 2I) The prognosis was not previously reported for patients with clinical taxonomy 2F—prolonged pain but no objective evidence

Summary

This retrospective study indicates that patients admitted to our CCU with a history typical for myocardial infarction appear to have a comparable in hospital mortality rate after 48 hours a comparable one year mortality rate and a comparable incidence of recurrent myocardial infarction during the *first year* whether or not they develop confirmatory ECG *or serum* enzyme changes Patients with chest pain typical of myocardial infarction who fail to develop confirmatory ECG or serum enzyme changes would appear to require the same care and follow up as do those patients admitted with chest pain who do develop such ECG or serum enzyme changes

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REFERENCES

1 Hurst J W The heart ed 3 New York 1974 McGraw Hill Book Company Inc p 1039
2. Weinblatt E Shapiro S Frank C W and Sager R V Prognosis of men after first myocardial infarction *Mortality and first recurrence in relation to selected* parameters Am J Pub Health 68 1379 1968
3 Murnaghan D Hickey N and Mulcahy R Immediate and long term experience of acute coronary insufficiency abstracted, Br Heart J 32 55 1970
4 Vakil, R M Pre infarction syndrome Management and *follow up* Am J Cardiol 14 55 1964
5 Lopes, M F Spivak, A P Harrison D C and Schroeder J S Prognosis in coronary care unit non infarction cases, *J A M A 228* 1558 1974
6 Krauss K R Hutter A M and DeSanctis R W Acute coronary insufficiency Course and follow up Arch Intern Med 129 808 19 2
7 Kannel W B and Feinleib M Natural history of angina pectoris in the Framingham Study Prognosis and survival, Am J Cardiol 29 154 1972
8 Norris, R M Caughey D E Mercer C J and Scott P J Prognosis after myocardial infarction Br Heart J *36* 786 *1974*
9 Norris, R M Caughey D E Mercer C J Deeming L W and Scott P J Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. Lancet 2 485 1970
10 Thygesen K Dalsgaard P., and Nielsen B L Prognosis after first myocardial infarction Acta Med Scand. 195 253 1974
11 Gazes, P C., Mobley E M Faris H M Duncan R C *and Humphries, G B Preinfarctional (unstable) angi*na—A pro pe tive study—Ten year *follow up* Circulation 48 331 1973
[illegible] Sigler L. H Prognosis of angina pectoris and myocardial infarction Further report Am J Cardiol 6 255 1960
[illegible] Sigler L. H Prognosis of angina pectoris and coronary occlusion Follow up of 1 00 cases J A M A 146 998 1951
14 Fulton M Duncan [illegible] Lutz W Donald [illegible] W., Kirby B J Morrison S L., Kerr F Julian D G and Oliver M F Natural history of unstable angina, Lancet 1 860 1972

Correlation coefficients for electrocardiographic and constitutional variables

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The first step in interpreting an electrocardiogram (ECG) is to determine whether it is normal or abnormal For this purpose reliable normal ranges of ECG measurements must be established These normal ECG ranges should be as narrow as possible because the narrower the normal range the more efficient the separation between normal and abnormal ECG s In this regard corrected orthogonal lead systems are superior to the conventional 12 lead system because of their higher degree of accuracy in performance[1,2] The influence of noncardiac factors—such as constitutional variables sex age and race—upon normal ECG wave forms has been pointed out by several investigators Pipberger and his associates revealed that race is one of the important determinants of ECG wave form Since physical constitutions are more or less different with different races, it appears warranted to investigate the interrelationships between constitutional variables and ECG wave forms in each race The results of such studies will greatly contribute to a better evaluation of ECG studies reported from different countries This study was attempted because no such investigation has been so far made in Japanese populations

Method and materials

Records were taken from 300 normal subjects (male 204 female, 96) Their ages ranged from 20 to 77 years (mean male, 28 years female 31 years) The age distribution is given in Table I Selection of cases was based on complete history physical examination and routine laboratory tests Excluded were all patients with conditions which frequently predispose to cardiovascular abnormalities such as diabetes mellitus pulmonary disease renal disease hypertension anemia, collagen vascular disease or other types of peripheral vascular disease Subjects with heart rates outside the range of 60 to 100 beats per minute or with ECG evidence of ventricular

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Table I Age distribution of the subjects included in the study

	Age groups (yr)			
	≤ 24	*25–34*	*≥ 35*	*Total*
No of cases	77	118	105	300

Table II Number of correlation coefficients which were found greater than 0 145 between ECG measurements and the various constitutional variables

	Correlation coefficient			
	≥0 145 →0 199	*0 200 →0 299*	*0 300 →0 399*	*Total*
Chest transverse diameter	17	28	2	47
Chest sagittal diameter	14	11	1	26
Body height	16	23	17	56
Body weight	19	28	6	53
Chest circumference	18	19	1	38
Deviation from ideal body weight	10	3	1	14
SD/TD ratio	17	3	0	20
Age	33	6	0	39

The limit of 0 145 represents less than 1 per cent in an equal tail test of hypothesis P = 0

Table III Correlations between constitutional variables and scalar parameters of orthogonal ECG*

	TD	SD	Height	Weight	CC	DIW	SD/TD	Age
				+	+			+
P dur	+	+		+	+			
QRS dur	+	+	+	+				
Px positive dur	+	+				–		
Py positive amp				+				
Py positive dur	+	+		+				
Pz positive dur		+						
Pz negative dur		+		+	+			
Qy dur	+	+					–	–
Qz amp				+	+			
Qz dur	+	+		+	+			
Rx amp	+	+						–
Ry amp								–
Rz amp			+					
Sx amp	+	+	+			+		
Q/Ry ratio						–		
R/Sx ratio			–					–
Tx amp			+	+		–		–
Ty amp								
Tz amp			–	–	–			
Rx + Rz amp	+	+	+	+	+			
Rx peak time	+	+	+	+	+			
Ry peak time	+	+	+	+	+			
Rz peak time	+	+	+	+	+			
P/Ry ratio								+

Abbreviations TD = chest transverse diameter SD = chest sagittal diameter CC = chest circumference DIW = deviation from ideal body weight plus sign (+) = positive correlation minus sign (–) = negative correlation

Table IV Correlations between constitutional variables and vectorial parameters

	TD	SD	Height	Weight	CC	DIW	SD/TD	Age
QRS-loop (F) Max vec mag	+			+				–
QRS-loop (F) Max vec ang	–	–		–		–		–
QRS-loop (S) Max vec mag			+					–
QRS-loop (T) Max vec mag	+		+	+				
T loop (F) Max vec mag	+		+	+		–	–	–
T loop (F) Max vec ang				–	–	–		
T loop (S) Max vec mag	+		+	+	+	–		–
T loop (S) Max vec ang	+	+	+	+	+			+
T loop (T) Max vec mag	+		+	+	+			–
T loop (T) Max vec ang	+	+	+	+	+			+

conduction defects were also excluded The Frank lead system was used with chest electrodes placed in the fourth intercostal space Tracings were recorded on the three channel heat writing recorder and also on frequency modulated magnetic tape There were 131 different ECG measurements computed for each subject All the ECG measurements were manually performed Details were as follows measurements from scalar leads X Y and Z included amplitudes of P Q R S and T waves and durations of P and the QRS complex Furthermore amplitude ratios were determined for Q/R R/S and P/R For all the QRS measurements the PR segment served as baseline at the level of the first deflection of the QRS complex For the P wave the TP segment was used as baseline Maximal vectors for QRS and T loop were determined in three plane projections—frontal left sagittal and horizontal Amplitudes of instantaneous vectors were determined at fixed intervals of 0 01 second during QRS and 0 02 second inter

Table V Correlations between constitutional variables and time normalized ST T segment

	TD	*SD*	*Height*	*Weight*	*CC*	*DIW*	*SD/TD*	*Age*
1/8 ST Tx	+		+	+			−	−
2/8 ST Tx	+		+	+	+		−	−
3/8 ST Tx	+		+	+	+		−	−
4/8 ST Tx	+		+	+	+		−	−
5/8 ST Tx	+		+	+	+			−
6/8 ST Tx			+	+				−
1/8 ST Ty			+					
2/8 ST Ty			+				−	−
3/8 ST Ty			+				−	−
4/8 ST Ty			+			−		−
5/8 ST Ty			+			−		−
6/8 ST Ty						−		−
1/8 ST Tz	−		−	−	−		+	
2/8 ST Tz	−		−	−	−		+	
3/8 ST Tz	−	−	−	−	−			
4/8 ST Tz	−	−	−	−	−			
5/8 ST Tz	−	−	−	−	−			
6/8 ST Tz	−	−	−	−	−			

Table VI Correlations between body height and ECG measurements*

	Correlation coefficient	*154 (cm) (63)†*	*155–159 (cm) (50)*	*160–164 (cm) (56)*	*165–169 (cm) (67)*	*170 (cm) (64)*	*P subgroups 1 vs 5*
Scalar measurement							
Rx + Rz amplitude (mv)	0.161	1.88±0.54 0.91–3.63	1.85±0.45 1.17–3.13	2.17±0.51 1.28–3.33	2.23±0.52 1.34–3.53	2.20±0.53 1.25–3.13	< 0.001
Rz amplitude (mv)	0.204	0.82±0.28 0.17–1.40	0.85±0.29 0.35–1.60	1.00±0.29 0.46–1.60	1.03±0.35 0.48–1.83	1.03±0.36 0.50–1.93	< 0.001
Sx amplitude (mv)	0.235	0.16±0.11 0.02–0.38	0.23±0.17 0.02–0.60	0.22±0.16 0.03–0.56	0.27±0.20 0.03–0.88	0.28±0.19 0.05–0.75	< 0.001
Tx amplitude (mv)	0.165	0.34±0.17 0.09–0.76	0.41±0.17 0.15–0.78	0.46±0.18 0.08–0.86	0.45±0.18 0.12–0.82	0.47±0.17 0.23–0.85	< 0.001
Tz amplitude (mv)	−0.300	−0.19±0.19 −0.55–0.18	−0.25±0.20 −0.60–0.11	−0.34±0.25 −0.78–0.40	−0.40±0.20 −0.74–0.34	−0.40±0.23 −0.75–0.28	< 0.001
0.02 sec ST Tx (mv)	0.215	0.01±0.03 −0.07–0.08	0.03±0.04 −0.04–0.12	0.03±0.03 −0.04–0.08	0.04±0.03 −0.02–0.10	0.04±0.04 −0.02–0.13	< 0.001
0.02 sec ST Ty (mv)	0.217	0.01±0.04 −0.08–0.07	0.02±0.04 −0.04–0.08	0.02±0.04 −0.08–0.10	0.03±0.03 [illegible]–0.10	0.03±0.04 −0.08–0.10	< 0.001
0.02 sec ST Tz (mv)	−0.310	−0.06±0.04 −0.15–0	−0.07±0.04 −0.04–0	−0.10±0.04 −0.20–−0.04	−0.11±0.04 −0.20–−0.03	−0.11±0.05 −0.23–0.03	< 0.001
0.04 sec ST Tx (mv)	0.258	0.03±0.03 −0.04–0.09	0.04±0.04 −0.02–0.15	0.05±0.04 −0.02–0.13	0.06±0.03 0–0.13	0.06±0.04 [illegible]–0.15	< 0.001
0.04 sec ST Ty (mv)	0.245	0.01±0.04 −0.07–0.08	0.02±0.03 −0.04–0.08	0.02±0.03 −0.05–0.10	0.03±0.03 −0.05–0.10	0.04±0.04 −0.05–0.10	< 0.001
0.04 sec ST Tz (mv)	−0.359	0.08±0.04 −0.18–0.01	−0.09±0.04 −0.18–−0.03	−0.12±0.04 −0.23–−0.06	−0.13±0.04 −0.20–−0.05	−0.14±0.05 −0.30–−0.02	< 0.001
1/8 ST Tx (mv)	0.264	0.03±0.03 −0.04–0.08	0.04±0.04 −0.03–0.13	0.05±0.04 −0.02–0.12	0.05±0.04 −0.02–0.13	0.06±0.04 0–0.17	< 0.001
1/8 ST Ty (mv)	0.250	0.01±0.04 −0.07–0.08	0.02±0.03 −0.04–0.08	0.02±0.04 −0.05–0.10	0.03±0.03 −0.05–0.10	0.04±0.03 −0.04–0.10	< 0.001

*The means and standard deviations in this and the following tables are shown in the upper line of each measurement. The lower line indicates the limits of 96 percentile ranges. In the last column results of t tests are given comparing the first and the last subgroups.

†Numbers in parentheses indicate numbers of cases

Table VI cont d

	Correlation coefficient	*154 (cm) (63)†*	*155 159 (cm) (50)*	*160-164 (cm) (56)*	*165 169 (cm) (67)*	*170 (cm) (64)*	*P subgroups 1 vs 5*
1/8 ST Tz (mv)	−0 353	−0 08±0 04 −0 18 −0 01	−0 09±0 04 −0 18 – −0 03	−0 13±0 04 −0 23 – −0 06	−0 13+0 04 −0 20 −0 06	−0 14±0 05 −0.30 −0 02	< 0 001
2 8 ST Tx (m)	0 ?69	0 05±0 04 −0 03±0 14	0 07±0 05 0 0 20	0 09±0 05 0 – 0 18	0 09±0 05 0 03 0 20	0 10±0 06 0 0? – 0 20	< 0 001
8 ST Ty (mv)	0 ?37	0 03±0 04 −0 05 0 10	0 04±0 04 −0 03 0 10	0 05±0 04 −0 04 0 12	0 05±0 04 −0 03 0 14	0 06+0 04 −0 02 0 14	< 0 001
/8 ST Tz (mv)	−0 3 2	−0 10±0 06 −0 ,5 −0 01	−0 12±0 06 −0 25 −0 03	−0 16±0 06 −0 30 −0 08	−0 17±0 05 −0 28 −0 06	−0 18±0 07 −0 35 −0 05	< 0 001
3/8 ST Tx (mv)	0 ? 1	0 09±0 06 −0 03 0 ?3	0 13±0 08 0 – 0 30	0 15±0 07 0 0? 0.28	0 16±0 0, 0 05 0 30	0 17±0 08 0 04 – 0 35	< 0 001
3/8 ST Ty (mv)	0 ?90	0 05±0 05 −0 03 0 18	0 07±0 04 −0 03 – 0 17	0 08±0 05 0 0 21	0 09±0 05 0 0 20	0 11±0 06 0 01 0 23	< 0 001
3 8 ST Tz (mv)	−0 381	−0 14±0 08 −0 38 −0 03	−0 16±0 09 −0 3, −0 04	−0 23±0 09 −0 43 −0 10	−0.24±0 08 −0 43 −0 09	−0.26±0 10 −0 45 −0 08	<0 001
Planar mea urements							
QRS loop (T) Max c mag (m)	0 145	1 02 0 31 0.53 1 96	0 94 0 33 0 ?, ?06	1 41 0 38 0 63 2 17	1 45 0 36 0 9 2 29	1 45±0 40 0 ?8 2 38	<0 01
T loop (F) Max vc mag (mv)	0 151	0 40±0 15 0 19 0 80	0 43±0 19 0 ?1 0 8?	0 48+0 15 0 15 0 84	0 49±0 1, 0 0 0 91	0 53±0 15 0.31 0.88	<0 001
T loop (S) Max c mag (m)	0 315	0 31±0 14 0 1? 0 60	0 36±0 15 0 12 0 65	0 45±0 15 0 13 0.83	0 46±0 15 0 ,0 – 0 ,3	0 47±0 16 0.24 0 75	<0.001
T loop (f) Max vc mag (mv)	0 28?	0 34+0 15 0 14 0 80	0 44±0 17 0 21 0 90	0 52±0 17 0 26 – 0.89	0 52±0 16 0 27 – 0.95	0 56±0 17 0 29 0.93	<0 001
T loop (T) Max ang (degrees)	0 304	?4+27 −20 0	?7±19 −6 58	40±16 10 0	42±16 0 76	39±14 18 71	<0 001

vals during the ST segment Five such instantaneous QRS vectors were taken after the onset and before the end of the QRS In order to improve comparability of instantaneous ST T vectors between different subjects the ST segment and T wave were normalized in time by dividing into eight equal parts (1/8 ST T 2/8 ST T 3/8 ST T 4/8 ST T 5/8 ST T 6/8 ST T 7/8 ST T 8/8 ST T)

Noncardiac factors used for correlations with ECG measurements included body height (HT) body weight (WT) deviation from ideal body weight (DIW) chest transverse diameter (TD) chest sagittal diameter (SD) SD/TD ratio chest circumference (CC) age and sex For correlations of ECG measurements with HT five subgroups were formed with the following height ranges (1) less than 154 cm (2) 155 to 159 cm (3) 160 to 164 cm (4) 165 to 169 cm (5) 170 cm or more WT was also divided into five subgroups (1) less than 49 Kg (2) 50 to 54 Kg (3) 55 to 59 Kg (4) 60 to 64 Kg (5) 65 Kg or more

Since the vast majority of ECG measurements are not normally distributed 96 percentile ranges were computed for all the measurements Selection of items for tabulation in this study was based upon practical considerations Correlation coefficients were calculated between each ECG measurement and the noncardiac parameters under study The significance of differences between subdivisions of groups was checked by t tests which served as a crude guide for detecting trends All the statistical calculations were performed with a digital computer

Results

Correlation coefficients between constitutional variables and ECG measurements are summarized in Table II The total number of coefficients above 0 145 represents less than 1 per cent in an

Table VII Correlation between body weight and ECG measurements*

	Correlation coefficient	≤49 (kg) (70)†	50-54 (kg) (60)	55-59 (kg) (60)	60-64 (kg) (52)	≥65 (kg) (58)	P sub groups 1 vs 5
Scalar measurements							
Rx+Rz amplitude (mv)	0.302	1.81±0.45 1.07-2.78	1.97±0.58 0.69-3.63	2.22±0.50 1.47-3.50	2.15±0.44 1.36-3.03	2.28±0.55 1.34-3.40	<0.001
Rx amplitude (mv)	0.303	0.95±0.33 0.40-2.08	1.03±0.39 0.40-2.23	1.20±0.38 0.53-1.97	1.22±0.35 0.60-1.83	1.27±0.43 0.58-2.35	<0.001
Tx amplitude (mv)	0.236	0.35±0.14 0.11-0.63	0.40±0.17 0.18-0.74	0.46±0.18 0.09-0.82	0.49±0.21 0.12-0.96	0.46±0.16 0.18-0.82	<0.001
Tz amplitude (mv)	-0.190	-0.23±0.18 -0.57-0.18	-0.30±0.26 -0.74-0.40	-0.34±0.25 -0.75-0.30	-0.41±0.16 -0.74--0.08	-0.35±0.24 -0.70-0.34	<0.001
0.04 sec (B) QRSx (mv)	0.256	0.73±0.39 0.02-1.88	0.85±0.41 0.11-1.87	0.99±0.40 0.30-1.97	1.01±0.43 0.22-1.76	1.04±0.48 0.25-2.25	<0.001
0.04 sec (B) QRSz (mv)	-0.160	0.44±0.39 -0.30-1.04	0.33±0.48 -0.78-1.29	0.42±0.47 -0.52-1.5[illegible]	0.25±0.52 -0.63-1.48	0.23±0.52 -0.80-1.33	<0.05
1/8 ST Tx (mv)	0.243	0.03±0.03 -0.04-0.133	0.05±0.03 -0.03-0.11	0.05±0.04 -0.02-0.15	0.05±0.04 -0.02-0.12	0.06±0.03 0-0.13	<0.001
1/8 ST Tz (mv)	-0.245	-0.08±0.04 -0.20--0.02	-0.12±0.05 -0.25--0.03	-0.13±0.05 -0.25--0.04	-0.13±0.04 -0.20--0.04	-0.12±0.04 -0.20--0.02	<0.001
2/8 ST Tx (mv)	0.298	0.05±0.04 -0.03-0.15	0.07±0.05 0-0.15	0.09±0.06 0-0.20	0.10±0.06 0.02-0.18	0.10±0.04 0.03-0.20	<0.001
2/8 ST Tz (mv)	-0.267	-0.11±0.05 -0.26--0.03	-0.15±0.07 -0.35--0.03	-0.16±0.08 -0.32--0.04	-0.18±0.06 -0.28--0.04	-0.17±0.05 -0.25--0.05	<0.001
3/8 ST Tx (mv)	0.318	0.09±0.06 0-0.23	0.13±0.07 0.03-0.26	0.16±0.08 0.02-0.33	0.17±0.09 0.04-0.35	0.16±0.06 0.05-0.30	<0.001
3/8 ST Tz (mv)	-0.272	-0.14±0.08 -0.36--0.03	-0.21±0.10 -0.45--0.05	-0.21±0.11 -0.43--0.06	-0.24±0.09 -0.43--0.07	-0.23±0.08 -0.40--0.08	<0.001
Planar measurements							
QRS loop (F) Max vc mag (mv)	0.199	1.34±0.36 0.81-2.31	1.40±0.48 0.65-2.57	1.61±0.38 0.94-2.38	1.58±0.41 0.91-2.43	1.56±0.44 0.88-2.44	<0.01
QRS loop (T) Max vc mag (mv)	0.242	1.20±0.34 0.64-2.13	1.31±0.44 0.63-2.44	1.45±0.37 0.82-2.27	1.41±0.36 0.82-2.27	1.46±0.37 0.78-2.20	<0.001
QRS loop (F) Max vc ang (degrees)	-0.191	47±14 24-80	48±22 22-86	45±12 22-74	44±28 22-64	37±14 16-70	<0.001
T loop (F) Max vc mag (mv)	0.190	0.40±0.14 0.16-0.71	0.46±0.12 0.27-0.67	0.50±0.18 0.19-1.00	0.54±0.20 0.21-0.91	0.47±0.15 0.28-0.80	<0.01
T loop (T) Max vc mag (mv)	0.284	0.38±0.15 0.14-0.80	0.47±0.02 0.21-0.7[illegible]	0.53±0.19 0.23-0.95	0.57±0.20 0.30-0.95	0.52±0.16 0.28-0.83	<0.001
T loop (F) Max vc ang (degrees)	-0.214	38±10 16-65	40±21 18-64	37±10 22-60	33±9 18-52	31±12 5-56	<0.001
T loop (T) Max vc ang (degrees)	0.191	26±22 -20-66	39±23 -3-62	35±21 -6-67	37±16 6-76	40±15 18-71	<0.001

*See note under Table VI
†Numbers of cases.

equal tail test of hypothesis P=0 on the basis of 300 subjects Such low values indicate only that a relationship exists that is not solely due to chance ($P < 0.01$) In reality higher coefficients are required for subgroups to be efficiently separated from each other As shown in Table II the highest correlations were found with HT with 1[illegible] coefficients exceeding 0.3 The next highest corre[illegible] lations were found with WT with 6 coefficient[illegible] above 0.3 Although substantial differences coul[illegible] be found between records classified according t[illegible] TD CC and age the magnitude of these differ[illegible]

Table VIII Comparison between men and women

	Men (204)†	Women (96)	P sub groups 1 vs 5
Scalar measurements			
Rx+Rz amplitude (mv)	2.18±0.53 1.45 3.40	1.85±0.47 1.07–3.10	<0.001
Qz, amplitude (mv)	0.60±0.27 0.15 1.29	0.48±0.02 0.18–0.92	<0.001
Rz amplitude (mv)	1.19±0.41 0.47 2.20	1.00±0.03 0.46 1.67	<0.001
Rz, amplitude (mv)	1.00±0.33 0.43–1.83	0.85±0.30 0.27 1.60	<0.001
Sx amplitude (mv)	0.2 ±0.19 0.03 0.5 (166)	0.16±0.11 0.01 0.40 (2)	<0.001
Tx amplitude (mv)	0.46±0.18 0.18 0.86	0.35±0.16 0.11 0.65	<0.001
Ty amplitude (mv)	0.34±0.13 0.10 0.60	0.27±0.12 0.03 0.49	<0.001
Tz amplitude (mv)	–0.39±0.22 –0.5 0.38	–0.17±0.16 –0.47 0.18	<0.001
0.04 sec (B) QRSx (mv)	0.97±0.45 0.0 .00	0.81±0.39 0.15 1.66	<0.01
0.04 sec (B) QRSz, (mv)	0.30±0.52 –0.8 1.47	0.42±0.36 –0.29 1.08	<0.05
0.02 sec ST Tx (mv)	0.04±0.03 –0.03 0.12	0.01±0.03 –0.07 0.09	<0.001
0.02 sec ST Ty (mv)	0.03±0.04 –0.06 0.10	0.01±0.03 –0.08 0.08	<0.001
0.02 sec ST Tz (mv)	–0.11±0.04 –0.21 –0.04	–0.06±0.03 –0.13 0	<0.001
0.04 sec ST Tx (mv)	0.06±0.04 –0.01 0.13	0.03±0.04 –0.04 0.11	<0.001
0.04 sec ST Ty (mv)	0.03±0.04 –0.05 0.10	0.01±0.04 –0.07 0.08	<0.001
0.04 sec ST Tz (mv)	–0.13±0.04 –0.23 –0.06	–0.07±0.03 –0.15 –0.01	<0.001

See legend Table VI
†Numbers of cases

Table VIII cont'd

	Men (204)†	Women (96)	P sub groups 1 vs 5
1/8 ST Tx (mv)	0.06±0.04 –0.02 0.14	0.03±0.03 –0.04 0.11	<0.001
1/8 ST Ty (mv)	0.03±0.04 –0.05 0.10	0.01±0.04 –0.07 0.08	<0.001
1/8 ST Tz (mv)	–0.13±0.04 –0.25 –0.06	–0.07±0.04 –0.15 –0.01	<0.001
2/8 ST Tx (mv)	0.10±0.05 –0.01 0.20	0.05±0.04 –0.03 0.14	<0.001
2/8 ST Ty (mv)	0.05±0.04 –0.03 0.14	0.03±0.04 –0.04 0.10	<0.001
2/8 ST Tz (mv)	–0.18±0.06 –0.32 –0.08	–0.09±0.05 –0.22 –0.03	<0.001
Planar measurements			
QRS-loop (F) Max vc mag (mv)	1.55±0.44 0.65 2.50	1.36±0.37 0.82 2.23	<0.001
QRS loop (S) Max vc mag (mv)	1.39±0.44 0.65±2.50	1.25±0.36 0.72 2.07	<0.001
QRS-loop (T) Max vc mag (mv)	1.43±0.39 0.72–2.38	1.20±0.33 0.0 1.93	<0.001
T loop (F) Max vc mag (mv)	0.50±0.17 0.21 0.88	0.40±0.12 0.19 0.63	<0.001
T loop (S) Max vc ma (mv)	0.48±0.15 0.23 0.83	0.29±0.11 0.12 0.51	<0.001
T loop (T) Max vc mag (mv)	0.55±0.17 0.28 0.91	0.36±0.13 0.16 0.57	<0.001
T loop (S) Max vc ang (degrees)	144±18 104 1.2	114±26 57 161	<0.001
T loop (T) Max vc ang (degrees)	42±14 18 .1	19±23 –0 60	<0.001

ences was relatively small DIW and SD/TD ratio revealed a weak correlation

General information on the presence or absence of the correlations is shown in Tables III to V in which the plus sign indicates positive correlation and the minus sign negative correlation

Body height (HT) The data obtained in this study show that HT is the most important determinant of the ECG Of the total 131 ECG items 56 (42.7 per cent) showed a significant correlation coefficient above 0.145 Trends of ECG measurements related to HT are shown in Table VI In this and the following table only those ECG items are listed where stratification of data appeared both feasible and practical As shown in Tables II through VI the most prominent height changes were found in amplitude measurements For example the mean value of

Table IX Correlation between age and ECG measurements*

	Correlation coefficient	≤ 24 (77)†	25–34 (118)	≥ 35 (105)	P subgroups 1 vs 3
Scalar measurements					
Qz amplitude (mv)	−0 195	0 59 ± 0 24 0 28 – 1 16	0 58 ± 0 27 0 10 – 1 16	0 51 ± 0 23 0 13 – 1 04	< 0 05
Ry amplitude (mv)	−0 241	1 12 ± 0 41 0 48 – 2 03	1 11 ± 0 32 0 52 – 1 74	0 98 ± 0 38 0 33 – 1 84	< 0 05
Tx amplitude (mv)	−0 198	0 46 ± 0 17 0 19 – 0 80	0 43 ± 0 17 0 11 – 0 98	0 40 ± 0 19 0 09 – 0 90	< 0 05
Ty amplitude (mv)	−0 213	0 34 ± 0 13 0 12 – 0 60	0 32 ± 0 13 0 10 – 0 57	0 29 ± 0 13 0 03 – 0 53	< 0 05
0 04 sec (B) QRSv (mv)	−0 236	0 87 ± 0 46 0 10 – 1 91	0 88 ± 0 34 0 20 – 1 56	0 74 ± 0 40 0 – 1 63	< 0 05
Planar measurements					
QRS loop (S) Max vc mag (mv)	−0 247	1 39 ± 0 42 0 76 – 2 27	1 41 ± 0 40 0 80 – 2 56	1 24 ± 0 41 0 65 – 2 17	< 0 05
QRS loop (F) Max vc mag (degrees)	−0 217	49 ± 24 23 – 80	45 ± 13 22 – 69	40 ± 19 17 – 76	< 0 01
T loop (F) Max vc mag (mv)	−0 235	0 49 ± 0 17 0 26 – 0 80	0 48 ± 0 17 0 17 – 0 91	0 43 ± 0 15 0 19 – 0 83	< 0 01
T loop (T) Max vc ang (degrees)	0 162	28 ± 17 −1 58	37 ± 20 −6 – 76	38 ± 22 −8 – 71	< 0 001

*See note under Table VI
†Numbers of cases

the sum of Rx and Rz (Rx + Rz) increased from 1 88 mv at 150 cm and below to 2 20 mv at 170 cm and above Identical changes were also apparent in magnitudes of Rz Sx Tx and Tz More conspicuous height changes were found in the ST T measurements with the maximal changes in the area between the beginning of the ST segment and the upstroke of the T wave In plane projection the magnitude of the maximal QRS vector in the transverse plane and the amplitude of the maximal T vector in the three planes tended to be augmented with an increase in HT

Body weight (WT) ECG measurements related to WT are listed in Table VII Many of the changes accompanying an increase in WT paralleled those of increasing HT For instance the mean value of Rx + Rz amplitudes increased from 1 81 mv at 49 Kg and below to 2 28 mv at 65 Kg and above The same trend was observed in magnitudes of Rx Tx and Tz Another important trend was seen in the measurements of the ST T in Leads X and Z These parameters especially in the area between the beginning of the ST segment and the upstroke of the T wave were increased in parallel with WT In the plane projection the magnitude of the maximal QRS vector was increased in both the transverse and the frontal plane The maximal T vectors in the transverse and the frontal planes were increased in magnitude and shifted in both anterior and superior directions

Chest transverse diameter (TD) A large number of ECG measurements correlated with TD but the significance level of these correlations was considerably lower than those for HT and WT A tabulation of results did not appear warranted therefore Suffice it to mention that an increase in TD led to a significant increase in QRS duration and to a superior and anterior shift of the maximal T vector

Sex Of 131 ECG items 61 (46 per cent) showed a statistically significant difference between men and women at the 0 01 level ($P < 0\ 01$) Several of these which would facilitate routine application of the findings are listed in Table VIII Amplitudes of Qz Rx Rz and Sx were found to be significantly larger in men The upper limits of the ranges of Rx differed by as much as 0 53 mv with the larger amplitudes always encountered in men The T wave amplitudes in the three scalar leads were also substantially larger in men Differences in mean amplitude of ST T time normalized instantaneous vectors between men and women

are shown in Fig 1 As shown in this figure ranges of ST T amplitude measurements in men were larger than those in women In planar projection the magnitudes of the maximal QRS and T vectors in the three planes were statistically larger in men

Age As shown in Table IX correlations with age were found to be less significant than those with HT WT and TD However from a practical point of view it is of value to mention that the magnitudes of Qz Ry Tx and Ty tended to diminish with increasing age These trends were reflected in the planar projections by a reduction in the magnitudes of the maximal QRS vector in the sagittal plane and of the maximal T vector in the frontal plane with rising age

Chest circumference (CC) A large number of ECG measurements correlated with CC But the significance levels of these correlations were considerably lower than those for HT and WT Then tabulation of results was omitted It is worthwhile however to make a brief comment that magnitudes of Rx Rz 2/8 ST Tx 2/8 ST Tz and 3/8 ST Tz were augmented in parallel with increasing CC

Chest sagittal diameter (SD) and SD/TD ratio General trends can be seen in Tables II through VI Since two parameters showed less significant correlations than TD tabulation of results was omitted

Deviation from ideal body weight (DIW) This parameter revealed less significant correlation with WT It is of interest that R/Sy ratio and Ty amplitude decreased with an increase in DIW which trends could not be obtained from WT It should be pointed out that the magnitudes of the maximal T vectors in the frontal and sagittal planes decreased with an increase with DIW whereas these two parameters increased with increasing WT

Discussion

It has been demonstrated clinically that an ECG wave form may be influenced by age sex race and constitutional variables such as body height (HT) body weight (WT) and chest configurations A clear understanding of normal ECG range determined by each of the factors which will affect normal ECG wave forms may open up a way to a better separation between normal and abnormal ECG s. The most extensive correlations between constitutional variables and the ECG

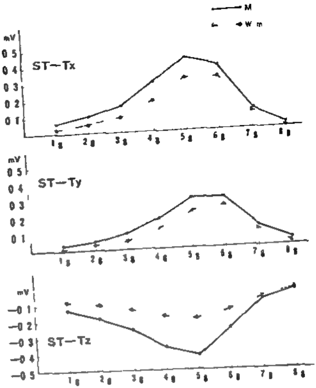

Fig 1 Comparison of mean magnitudes of instantaneous ST T vectors between men and women Magnitudes of ST T vectors in three scalar leads especially in leads X and Z were greater in men than in women Significance of these prominent differences is discussed in the text

wave forms have been reported by Simonson [3] whose investigation was primarily based on the conventional 12 lead recordings With the use of a corrected orthogonal lead system correlations with chest configuration and ponderal index have been reported by Barun and his co workers [1] Their correlational study in which only the scalar lead deflections were included demonstrated that ECG wave forms were most strongly influenced by age This finding is in accord with those of Pipberger and his associates who stated that age revealed a significant correlation coefficient in 89 out of 333 different ECG measurements (26 7 per cent) They emphasized that the amplitude of a large number of QRS and ST T parameters was decreased with advancing age and also demonstrated that age changes of the ECG were already highly significant after age 30 with an almost uniform increase up to the late decades of life Although nearly identical trends of age change of the ECG were obtained from this study HT and WT revealed stronger influences upon the ECG than age The failure to detect a

Table IX Correlation between age and ECG measurements*

	Correlation coefficient	*≤ 24 (77)†*	*25–34 (118)*	*≥ 35 (105)*	*P subgroups 1 vs 5*
Scalar measurements					
Qz amplitude (mv)	−0.195	0.59±0.24 0.28–1.16	0.58±0.27 0.10–1.16	0.51±0.23 0.13–1.04	<0.05
Ry amplitude (mv)	−0.241	1.12±0.41 0.48–2.03	1.11±0.32 0.52–1.74	0.98±0.38 0.33–1.84	<0.05
Tx amplitude (mv)	−0.198	0.46±0.17 0.19–0.80	0.43±0.17 0.11–0.98	0.40±0.19 0.09–0.90	<0.05
Ty amplitude (mv)	−0.213	0.34±0.13 0.12–0.60	0.32±0.13 0.10–0.57	0.29±0.13 0.03–0.53	<0.05
0.04 sec (B) QRSy (mv)	−0.236	0.87±0.46 0.10–1.91	0.88±0.34 0.20–1.56	0.74±0.40 0–1.63	<0.05
Planar measurements					
QRS loop (S) Max vc mag (mv)	−0.247	1.39±0.42 0.76–2.27	1.41±0.40 0.80–2.56	1.24±0.41 0.65–2.17	<0.05
QRS loop (F) Max vc mag (degrees)	−0.217	49±24 23–80	45±13 22–69	40±19 17–76	<0.01
T loop (F) Max vc mag (mv)	−0.235	0.49±0.17 0.26–0.80	0.48±0.17 0.17–0.91	0.43±0.15 0.19–0.83	<0.01
T loop (T) Max vc ang (degrees)	0.162	28±17 −1–58	37±20 −6–76	38±22 −8–71	<0.001

*See note under Table VI
†Numbers of cases

the sum of Rx and Rz (Rx + Rz) increased from 1.88 mv at 150 cm and below to 2.20 mv at 170 cm and above. Identical changes were also apparent in magnitudes of Rz, Sx, Tx and Tz. More conspicuous height changes were found in the ST-T measurements, with the maximal changes in the area between the beginning of the ST segment and the upstroke of the T wave. In plane projection, the magnitude of the maximal QRS vector in the transverse plane and the amplitude of the maximal T vector in the three planes tended to be augmented with an increase in HT.

Body weight (WT) ECG measurements related to WT are listed in Table VII. Many of the changes accompanying an increase in WT paralleled those of increasing HT. For instance, the mean value of Rx + Rz amplitudes increased from 1.81 mv at 49 Kg and below to 2.28 mv at 65 Kg and above. The same trend was observed in magnitudes of Rx, Tx and Tz. Another important trend was seen in the measurements of the ST-T in Leads X and Z. These parameters, especially in the area between the beginning of the ST segment and the upstroke of the T wave, were increased in parallel with WT. In the plane projection, the magnitude of the maximal QRS vector was increased in both the transverse and the frontal plane. The maximal T vectors in the transverse and the frontal planes were increased in magnitude and shifted in both anterior and superior directions.

Chest transverse diameter (TD) A large number of ECG measurements correlated with TD, but the significance level of these correlations was considerably lower than those for HT and WT. A tabulation of results did not appear warranted, therefore. Suffice it to mention that an increase in TD led to a significant increase in QRS duration and to a superior and anterior shift of the maximal T vector.

Sex Of 131 ECG items, 61 (46 per cent) showed a statistically significant difference between men and women at the 0.01 level ($P < 0.01$). Several of these, which would facilitate routine application of the findings, are listed in Table VIII. Amplitudes of Qz, Rx, Rz and Sx were found to be significantly larger in men. The upper limits of the ranges of Rx differed by as much as 0.53 mv, with the larger amplitudes always encountered in men. The T wave amplitudes in the three scalar leads were also substantially larger in men. Differences in mean amplitude of ST-T time-normalized instantaneous vectors between men and women

are shown in Fig 1 As shown in this figure ranges of ST T amplitude measurements in men were larger than those in women In planar projection the magnitudes of the maximal QRS and T vectors in the three planes were statistically larger in men

Age As shown in Table IX correlations with age were found to be less significant than those with HT WT and TD However from a practical point of view it is of value to mention that the magnitudes of Qz Ry Tx and Ty tended to diminish with increasing age These trends were reflected in the planar projections by a reduction in the magnitudes of the maximal QRS vector in the sagittal plane and of the maximal T vector in the frontal plane with rising age

Chest circumference (CC) A large number of ECG measurements correlated with CC But the significance levels of these correlations were considerably lower than those for HT and WT Then tabulation of results was omitted It is worthwhile however to make a brief comment that magnitudes of Rx Rz 2/8 ST Tx 2/8 ST Tz and 3/8 ST Tz were augmented in parallel with increasing CC

Chest sagittal diameter (SD) and SD/TD ratio General trends can be seen in Tables II through VI Since two parameters showed less significant correlations than TD tabulation of results was omitted

Deviation from ideal body weight (DIW) This parameter revealed less significant correlation with WT It is of interest that R/Sy ratio and Ty amplitude decreased with an increase in DIW which trends could not be obtained from WT It should be pointed out that the magnitudes of the maximal T vectors in the frontal and sagittal planes decreased with an increase with DIW whereas these two parameters increased with increasing WT

Discussion

It has been demonstrated clinically that an ECG wave form may be influenced by age sex race and constitutional variables such as body height (HT) body weight (WT) and chest configurations A clear understanding of normal ECG range determined by each of the factors which will affect normal ECG wave forms may open up a way to a better separation between normal and abnormal ECG s. The most extensive correlations between constitutional variables and the ECG

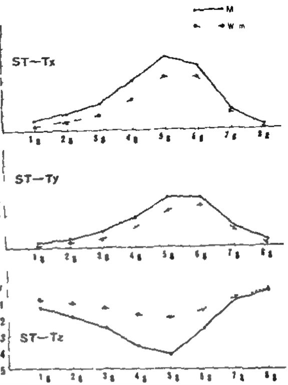

Fig 1 Comparison of mean magnitudes of instantaneous ST T vectors between men and women Magnitudes of ST T vectors in three scalar leads, especially in leads X and Z were greater in men than in women Significance of these prominent differences is discussed in the text

wave forms have been reported by Simonson[3] whose investigation was primarily based on the conventional 12 lead recordings With the use of a corrected orthogonal lead system correlations with chest configuration and ponderal index have been reported by Barun and his co workers[5] Their correlational study in which only the scalar lead deflections were included demonstrated that ECG wave forms were most strongly influenced by age This finding is in accord with those of Pipberger and his associates who stated that age revealed a significant correlation coefficient in 89 out of 333 different ECG measurements (26 7 per cent) They emphasized that the amplitude of a large number of QRS and ST T parameters was decreased with advancing age and also demonstrated that age changes of the ECG were already highly significant after age 30 with an almost uniform increase up to the late decades of life Although nearly identical trends of age change of the ECG were obtained from this study HT and WT revealed stronger influences upon the ECG than age The failure to detect a

Table IX Correlation between age and ECG measurements*

	Correlation coefficient	*≤ 24 (77)†*	*25–34 (118)*	*≥ 35 (105)*	*P subgroups 1 vs 5*
Scalar measurements					
Qz amplitude (mv)	−0.195	0.59 ± 0.24 0.28 − 1.16	0.58 ± 0.27 0.10 − 1.16	0.51 ± 0.23 0.13 − 1.04	< 0.05
Ry amplitude (mv)	−0.241	1.12 ± 0.41 0.48 − 2.03	1.11 ± 0.32 0.52 − 1.74	0.98 ± 0.38 0.33 − 1.84	< 0.05
Tx amplitude (mv)	−0.198	0.46 ± 0.17 0.19 − 0.80	0.43 ± 0.17 0.11 − 0.98	0.40 ± 0.19 0.09 − 0.90	< 0.05
Ty amplitude (mv)	−0.213	0.34 ± 0.13 0.12 − 0.60	0.32 ± 0.13 0.10 − 0.57	0.29 ± 0.13 0.03 − 0.53	< 0.05
0.04 sec (B) QRSy (mv)	−0.236	0.87 ± 0.46 0.10 − 1.91	0.88 ± 0.34 0.20 − 1.56	0.74 ± 0.40 0 − 1.63	< 0.05
Planar measurements					
QRS loop (S) Max vc mag (mv)	−0.247	1.39 ± 0.42 0.76 − 2.27	1.41 ± 0.40 0.80 − 2.56	1.24 ± 0.41 0.65 − 2.17	< 0.05
QRS loop (F) Max vc mag (degrees)	−0.217	49 ± 24 23 − 80	45 ± 13 22 − 69	40 ± 19 17 − 76	< 0.01
T loop (F) Max vc mag (mv)	−0.235	0.49 ± 0.17 0.26 − 0.80	0.48 ± 0.17 0.17 − 0.91	0.43 ± 0.15 0.19 − 0.83	< 0.01
T loop (T) Max vc ang (degrees)	0.162	28 ± 17 −1 − 58	37 ± 20 −6 − 76	38 ± 22 −8 − 71	< 0.001

*See note under Table VI
†Numbers of cases

the sum of Rx and Rz (Rx + Rz) increased from 1.88 mv at 150 cm and below to 2.20 mv at 170 cm and above. Identical changes were also apparent in magnitudes of Rz, Sx, Tx and Tz. More conspicuous height changes were found in the ST-T measurements with the maximal changes in the area between the beginning of the ST segment and the upstroke of the T wave. In plane projection, the magnitude of the maximal QRS vector in the transverse plane and the amplitude of the maximal T vector in the three planes tended to be augmented with an increase in HT.

Body weight (WT) ECG measurements related to WT are listed in Table VII. Many of the changes accompanying an increase in WT paralleled those of increasing HT. For instance, the mean value of Rx + Rz amplitudes increased from 1.81 mv at 49 Kg and below to 2.28 mv at 65 Kg and above. The same trend was observed in magnitudes of Rx, Tx and Tz. Another important trend was seen in the measurements of the ST-T in Leads X and Z. These parameters, especially in the area between the beginning of the ST segment and the upstroke of the T wave, were increased in parallel with WT. In the plane projection, the magnitude of the maximal QRS vector was increased in both the transverse and the frontal plane. The maximal T vectors in the transverse and the frontal planes were increased in magnitude and shifted in both anterior and superior directions.

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Sex Of 131 ECG items, 61 (46 per cent) showed a statistically significant difference between men and women at the 0.01 level ($P < 0.01$). Several of these which would facilitate routine application of the findings are listed in Table VIII. Amplitudes of Qz, Rx, Rz and Sx were found to be significantly larger in men. The upper limits of the ranges of Rx differed by as much as 0.53 mv, with the larger amplitudes always encountered in men. The T wave amplitudes in the three scalar leads were also substantially larger in men. Differences in mean amplitude of ST-T time-normalized instantaneous vectors between men and women

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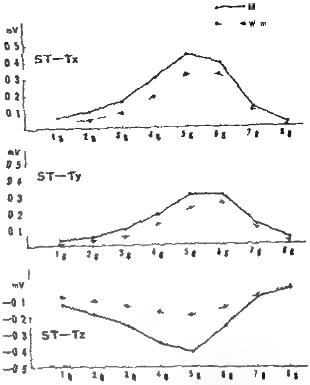

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had the effect of reducing the magnitude of many of the QRS and ST T measurements It is also of interest that a majority of the QRS and ST T parameters were larger in male than in female patients It should be emphasized from the results of this study that normal ECG criteria must be established for each ECG determinant

REFERENCES

1 Abild kov J A and Pence E D A comparative study of spatial vectorcardiogram obtained with equilateral tetrahedron and a corrected system of electrode placement, Circulation 13 63 19 6
2 Pipberger H V Bialek M Perloff J K and Schnaper H W Correlation of clinical information in the standard 1? lead ECG and in a corrected orthogonal 3 lead ECG Am Heart J 61 34 1961
3 Simonson E. Differentiation between normal and abnormal in electrocardiography St Louis. 1961 The C V Mosby Company
4 Simonson E Physiological variations in the genesis of the electrocardiogram *in* Rijlant P editor Processing of the XIIth International Colloquium Vectorcardiographicum Bruxelles 19 ? Presses Académiques Europeénnes, p 523
5 Barun E R., Chapman J M and Massey F J Electrocardiographic data recorded with Frank leads in subjects without cardiac disease and in subjects with left ventricular overload Am J Cardiol 18 656 1966
6 Pipberger H V Goldman M J Littmann D Murphy G P Cosma J., and Snyder J R Correlations of the orthogonal electrocardiogram and vectorcardiogram with constitutional variables in 518 normal men Circulation 35 536 1967
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highly significant effect of age upon the ECG measurements can be ascribed to the relatively younger ages of the populations in this study than those of other studies [1]

It should be pointed out that HT was found to be the strongest determinant of ECG and that amplitude of a large number of QRS and ST T parameters was significantly augmented with an increase in HT WT was also a powerful determinant and revealed a strong positive correlation with amplitude of a large number of QRS and ST T measurements These findings are in sharp contrast to those of Pipberger and his associates They demonstrated that the main ECG changes accompanied by increasing WT were a reduction in amplitude of QRS and ST T measurements and that these changes were quite similar to those of advancing age

Quite recently however Brohet and Tuna revealed that there was a trend toward a decrease of QRS amplitude after weight reduction These findings are quite in agreement with what was found in this study The discrepancy in results between these studies could not be easily explained It is of interest that ST T parameters in Lead Y were relatively free of influence by WT The next most important constitutional parameter was chest transverse diameter (TD) ECG changes accompanied by increasing TD were observed mainly in Leads X and Z The most prominent findings were increases in QRS duration and magnitude of 0 05 second QRS vector from its onset in Lead X and a reduction in magnitude of 0 04 second QRS vector from its onset in Lead Z ECG changes influenced by chest sagittal diameter (SD) and chest circumference (CC) were almost identical to those by TD though less remarkable but SD/TD ratio revealed less significant correlations with ECG measurements

Sex was found to be an important determinant of ECG Significant sex differences were observed in 61 of 131 scalar and vectorial items (46 per cent) Sotobata and his associates[1] reported that 43 of 64 vectorial items (67 per cent) showed significant sex differences This study clearly demonstrated that most of the ECG amplitudes of QRS and ST T parameters in men were significantly greater than those in women These findings are of great importance especially in diagnosis of ventricular hypertrophy and myocardial damage The application of normal ECG criteria obtained from a male dominated population to an ECG obtained from a female patient may increase the incidence of false positive indications of myocardial damage and of false negative indications of ventricular hypertrophy Along the same line of reasoning when normal ECG criteria obtained from a female dominated population are applied to an ECG from a male patient, this may increase the incidence of false negative indications of myocardial damage and of false positive indications of ventricular hypertrophy In order to avoid these faults, ECG normal ranges should be determined separately for the male population and for the female population

Conclusion

This study has shown that a great number of ECG measurements are influenced by various noncardiac parameters An ECG measurement when used for diagnosis should be corrected for each of these noncardiac factors A firm knowledge of normal ECG ranges determined by each of these noncardiac parameters will open up the way to a better understanding of ECG s

Summary

The influence of noncardiac factors such as constitutional variables sex and age upon the orthogonal electrocardiogram (ECG) and vectorcardiogram was investigated in 300 normal Japanese subjects Constitutional variables included body height (HT) body weight (WT) deviation from ideal body weight (DIW) chest transverse diameter (TD) chest sagittal diameter (SD) SD/TD ratio and chest circumference (CC) Among these constitutional variables HT was found to be the most important determinant of ECG followed by WT TD CC SD SD/TD ratio and DIW in that order An increase in HT resulted in the augmentation of magnitudes of a large number of the QRS and ST T parameters WT showed almost the same trends as HT Of the four measurements of the chest configuration under study TD proved to be the most powerful determinant An increase in TD led to a significant increase in QRS duration and to a superior and anterior shift of the maximal T vector The remaining constitutional variables revealed far less significant correlation with ECG measurements than did HT and WT Besides the constitutional variables sex and age were also proved to be important ECG determinants Advancing age

had the effect of reducing the magnitude of many of the QRS and ST T measurements It is also of interest that a majority of the QRS and ST T parameters were larger in male than in female patients It should be emphasized from the results of this study that normal ECG criteria must be established for each ECG determinant

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Living with prosthetic heart valves

SUBSEQUENT NONCARDIAC OPERATIONS AND THE RISK OF THROMBOEMBOLISM OR HEMORRHAGE

Richard E Katholi M D
Stanton P Nolan M D
Lockhart B McGuire, M D , F A C P
Charlottesville Virginia

Although the development of prosthetic heart valves is a major improvement in the treatment of valvular heart disease thromboembolism remains a frequent complication that accompanies the use of nonbiological prostheses Modification of the design of the prosthesis by covering the metal parts with fabric has not eliminated the problem of thromboembolism[1] and therefore long term anticoagulation is still employed to prevent this complication Long term anticoagulation introduces the hazard of hemorrhage either from an excessive anticoagulant effect or from subsequent operations

In order to assess the risk of thromboembolism and hemorrhage the course of 111 patients surviving valve replacement has been reviewed The average period of follow up was 4 years Episodes of thromboembolism and of hemorrhage were documented and evaluated in relation to the status of anticoagulation During this period 36 patients underwent 44 noncardiac operations or invasive diagnostic procedures The management of anticoagulation during each procedure and the resultant complications were analyzed Based on this analysis preliminary guidelines have been developed for the management of anticoagulants in patients with prosthetic valves who require subsequent noncardiac operations

From the Departments of Internal Medicine and Surgery University of Virginia Hospital Charlottesville Va

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Patients and methods

Between April, 1968 and August 1972 116 patients survived the operative replacement of the aortic mitral tricuspid or a combination of these valves at the University of Virginia Hospital Five patients were excluded because adequate late information could not be obtained All patients were seen annually in our cardiac clinic or more often depending on the level of surveillance provided by their regular physicians If a thromboembolic or hemorrhagic event was observed at another hospital details of the anatomic location the severity and the prothrombin time were provided by the local physicians whose collaboration permitted this study

A sudden vascular occlusive episode was considered to be embolic in origin Myocardial infarction however was not considered embolic if there was previous evidence of arteriosclerotic heart disease There was one instance of myocardial infarction without arteriosclerosis in a patient with an autopsy proved coronary embolism Emboli occurring within the first 10 days after valve insertion were not included Sodium warfarin was the anticoagulant employed in all of these patients and the objective of anticoagulation was to achieve a prothrombin time between 1 5 and 2 5 times the control sample

Aortic valve replacement was performed with a Starr Edwards Model 1200 prosthesis in 55 patients and with a Magovern aortic prosthesis in 19 patients In the mitral position Kay Shiley disc valves were used in 35 patients Starr Edwards Model 6120 valves in four and a Magovern mitral valve in one patient In the tricuspid position

Table I Incidence of thromboembolism

A Thromboembolism after aortic valve replacement	
Number of patients	71
Number of episodes	11
Incidence of thromboembolism	3 4
Anticoagulant status at time of thromboembolism	
Adequate†	2
Inadequate‡	6
Unknown	3
B Thromboembolism after mitral valve or combined valve replacements	
Number of patients	40
Number of episodes	28
Incidence of thromboembolism	15 2
Anticoagulant status at time of thromboembolism	
Adequate	13
Inadequate†	9
Unknown	6

P 1 000 patient months at risk
†Prothrombin time 1.5 to 2.5 times control
‡Prothrombin time < 1 5 times control

Table II Nonsurgical hemorrhage after heart valve replacement

Number of patients	111
Number of episodes	13
Incidence	2.1 3 1
Anticoagulant status at time of hemorrhage	
Adequate†	3
Excessive‡	9
Unknown	1

Pe 1 000 patient months at risk
†Prothrombin time 1.5 to 2 5 times control
‡Prothrombin time > 2.5 times control.

Table III Forty four subsequent noncardiac operations in patients with prosthetic valves

Major (22)	
Cholecystectomy	5
Pulse generator change	4
Colon resection	3
Hysterectomy	3
Pericardiectomy	1
Other	6
Minor (22)	
Biopsy excision aspiration	8
Arteriography	7
Dental extraction	5
Rectal polypectomy	1
Embolectomy	1

Kay Shiley valves were used in five patients and a Magovern mitral valve in one patient

Results

The average age of the 111 patients was 50 years and there were 73 men and 38 women In 71 patients only the aortic valve was replaced in 31 the mitral valve alone was replaced and nine patients received combined prostheses (mitral and tricuspid in six mitral and aortic in three) When their clinical courses were compared the patients with two prostheses were indistinguishable from those with an isolated mitral valve replacement For this reason these two groups of patients have been combined in this analysis

Thromboembolism In the 71 patients with isolated aortic valve replacement there were 11 embolic episodes that were unrelated to subsequent operations, or an incidence of 3 4 episodes per 1 000 patient months at risk (Table I A) All except two of these episodes occurred within the first 11 months after valve replacement The prothrombin time was measured at the time of embolism in eight of the 11 patients In six of the eight patients the level of anticoagulation was inadequate as defined by a prothrombin time of less than 1 5 times the control sample

Thromboembolism occurred 28 times in the 40 patients with mitral or combined prostheses or 15 2 episodes per 1 000 patient months at risk (Table I B) Inadequate anticoagulation was demonstrated in only nine of 22 patients in whom this information was available These incidents include two thromboemboli which occurred after deliberate discontinuation of sodium warfarin to allow the performance of subsequent operative procedures The 28 embolic episodes were evenly distributed throughout the period at risk and nine episodes occurred more than 48 months after valve replacement The patients with mitral or combined prostheses also differed from those with isolated aortic prostheses in the frequency of occurrence of chronic atrial fibrillation Atrial fibrillation was present in 29 (71 per cent) of the 40 patients with mitral and combined prostheses but in only six (8 per cent) of 71 patients with isolated aortic valve replacement

Of the total of 39 thromboemboli 33 (83 per cent) were cerebral in location with 25 of these resulting in minor or no residual neurological deficit

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Incidence of thromboembolism	15.2
Anticoagulant status at time of thromboembolism	
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Number of patients	111
Number of episodes	13
Incidence	2 1 3 1
Anticoagulant status at time of hemorrhage	
Adequate†	3
Excessive‡	9
Unknown	1

*Per 1 000 patient months at risk
†Prothrombin time 1.5 to 2.5 times control
‡Prothrombin time > 2.5 times control

Table III Forty four subsequent noncardiac operations in patients with prosthetic valves

Major (22)	
Cholecystectomy	5
Pulse generator change	4
Colon resection	3
Hysterectomy	3
Pericardiectomy	1
Other	6
Minor (22)	
Biopsy excision aspiration	8
Arteriography	7
Dental extraction	5
Rectal polypectomy	1
Embolectomy	1

15.2 episodes per 1 000 patient months at risk (Table I B) Inadequate anticoagulation was demonstrated in only nine of 22 patients in whom this information was available These incidents include two thromboemboli which occurred after deliberate discontinuation of sodium warfarin to allow the performance of subsequent operative procedures The 28 embolic episodes were evenly distributed throughout the period at risk and nine episodes occurred more than 48 months after valve replacement The patients with mitral or combined prostheses also differed from those with isolated aortic prostheses in the frequency of occurrence of chronic atrial fibrillation Atrial fibrillation was present in 29 (71 per cent) of the 40 patients with mitral and combined prostheses but in only six (8 per cent) of 71 patients with isolated aortic valve replacement

Of the total of 39 thromboemboli 33 (83 per cent) were cerebral in location with 25 of these resulting in minor or no residual neurological deficit

Table IV Anticoagulants discontinued or maintained

A Experience with 31 subsequent operations in patients with prosthetic aortic valves	
Anticoagulant discontinued in 25 operations	
Perioperative thromboembolism	0
Perioperative hemorrhage	0
Anticoagulant maintained in 6 operations	
Perioperative thromboembolism	0
Perioperative hemorrhage	3
B Experience with 13 subsequent operations in patients with prosthetic mitral valves and combined valve replacements	
Anticoagulant discontinued in 10 operations	
Perioperative thromboembolism	2
Perioperative hemorrhage	0
Anticoagulant maintained in 3 operations	
Perioperative thromboembolism	0
Perioperative hemorrhage	1

Table V Causes of late death after valve replacement

Aortic valve (71 patients 8 deaths)	
Coronary artery disease	3
Cause unknown	2
Bleeding & wound infection	1
Refractory heart failure	1
Other	1
Mitral valve (31 patients 11 deaths)	
Cerebral embolism	4
Refractory heart failure	2
Cause unknown	2
Other	2
Bacterial valvulitis	1
Combined valves (9 patients 3 deaths)	
Cerebral emboli m	1
Valve thrombosis	1
Coronary embolism	1

(Deaths after subsequent non cardiac operations)

Nonsurgical hemorrhage Among the total group of 111 patients receiving sodium warfarin there were 13 instances of documented hemorrhage which were unrelated to subsequent operations In Table II these patients have not been divided according to sites of valve replacement because there was no significant difference between the aortic valve group and the mitral/combined valve group in this respect After isolated aortic valve replacement the risk of spontaneous hemorrhage was 3 1 per 1 000 patient months and after mitral or combined valve replacement the risk of spontaneous hemorrhage was 2 1 per 1 000 patient months A prothrombin time greater than 2 5 times the control was demonstrated at the time of hemorrhage in nine of the 12 patients for whom this information was available None of these hemorrhagic episodes was fatal

Subsequent operative procedures Of the 44 subsequent operations 22 were major procedures and 22 were minor procedures (Table III) This distinction is based on a standard classification system by which an operation is major if either a body cavity or a bone is entered

In patients with isolated aortic valve replacement anticoagulants were discontinued prior to a subsequent operation 25 times and then resumed on the third to fifth postoperative day (Table IV A) There were no instances of perioperative thromboembolism or hemorrhage On the other hand when the anticoagulant was maintained in six patients there were three episodes of major perioperative hemorrhage All of these were sufficient to require unanticipated blood replacement and in one patient a hematoma at the site of a pulse generator implantation resulted in a fatal wound infection

Thirteen subsequent operations were performed on patients with mitral or combined prosthetic valves (Table IV, *B*) Anticoagulation was discontinued for 3 to 5 days in 10 instances prior to the operation in order to decrease perioperative bleeding There were two fatal perioperative thromboemboli One of these was an autopsy proved thrombosis of both aortic and mitral prostheses in a patient who had undergone a uterine dilatation and curettage 10 days earlier This patient had had no previous thromboembolic complications Significant bleeding occurred in one of the three patients in whom anticoagulation was maintained

Survival and causes of late deaths Table V indicates the causes of death for the 22 patients who died during the average period of 4 years after successful valve replacement The late mortality rate for patients with isolated aortic valve replacement was lower than for those with mitral and combined valve replacement None of the deaths in patients with aortic valve replacement could be attributed to thromboemboli In contrast seven of the 12 classifiable late deaths in patients with mitral and combined valve replacements were due to thromboembolism

Discussion

The assessment of reports of thromboembolism and of survival after prosthetic valve surgery requires consideration of (1) the model of prosthesis used (2) the site of valve replacement (3) the length of the follow up period and (4) the preoperative cardiac functional status of the patient From analyses of these various points general characteristics about caged ball and caged-disc prostheses have emerged

Aortic valve replacement Recent studies of patients undergoing isolated aortic valve replacement indicate that the operative mortality rate is less than 10 per cent and that the embolism rate is 5 to 10 per cent over a 3 to 5 year period The 16 per cent incidence of emboli over 4 years observed here or 3 4 embolic per 1 000 patient months at risk after isolated aortic valve replacement is higher than that described in the initial reports of cloth covered prostheses in the aortic position However a recent report indicates that 13 per cent of the patients with cloth covered valves will have emboli during the first 3 years without anticoagulation and concludes that there is a continuing need for anticoagulation The Starr Edwards and Magovern valves used during the present study were not cloth covered Our observation of a decreased prothrombin time associated with the majority of embolic episodes in patients with aortic prostheses (Table I A) supports the conclusion of Barnhorst and associates who found that embolism after aortic valve replacement was usually associated with an inadequate warfarin effect

In terms of anticoagulant related hemorrhage Friedli and associates found a 10 per cent incidence of significant bleeding and a 1 per cent fatality in 170 patients over a period of 2 years Shean and associates described minor anticoagulant complications in 18 4 per cent of 455 patients over a period of 3 years after aortic valve replacement Our results (Table II) represent a low incidence of hemorrhagic complications in both aortic and mitral and combined valve groups and when hemorrhage did occur it was usually associated with an excess sodium warfarin effect This finding was expected since sodium warfarin-related bleeding should be a function of the imprecise regulation of the drug and not of the antecedent cardiac status or of the type of prosthesis used

The total of eight deaths (11 per cent) in 71 patients during a 4 year period after aortic valve replacement (Table V) is similar to the previously reported mortality rates of 9 13 and 16 per cent during comparable time periods The most frequent cause of late death for survivors of aortic valve replacement in this and in other studies has been either coronary disease or unexplained sudden death in which coronary disease was suspected

Mitral and combined valve replacement All patients receiving combined prostheses in this series had mitral valve replacement plus either aortic or tricuspid valve replacement Therefore they have been combined with the patients receiving isolated mitral replacement for the purpose of this study In an analysis of multiple valve replacements the Portland group found the incidence of thromboembolism to be no different with multiple valves or with isolated mitral replacement

The patients in this study receiving mitral and combined prostheses had a fourfold greater incidence of thromboembolism than those with isolated aortic valve replacement Three other studies have confirmed the higher frequency of emboli associated with prostheses in the mitral position Nevertheless the incidence of thromboembolic in the present report is higher than was reported in three other studies in which Starr Edwards mitral prostheses were used Thirty five of the 40 mitral prostheses in the present study were Kay Shiley caged disc valves Messmer and colleagues compared several types of caged disc prostheses and found higher rates of embolism associated with the Kay Shiley valve The Mayo Clinic found a 40 per cent incidence of embolism during the first 4 years after insertion of uncovered ball valves in the mitral position however the incidence of thromboembolism was decreased when later model valves were used The Kay Shiley disc valve has not been used at the University of Virginia since 1972

Barnhorst and colleagues found that an increase in thromboembolism was associated with large left atria with left atrial thrombi found at operation and with inadequate anticoagulation An earlier study indicated that emboli occurred in 28 per cent of patients with atrial fibrillation and in only 19 per cent of patients with normal sinus rhythm Atrial fibrillation was present in 29 of our 40 patients with mitral and combined valve prostheses Thus our high rate of embolism may

reflect either a difference in cardiac rhythm and heart size or a defect in the design of the prosthesis In summary embolism after mitral valve replacement appears to have several, independent contributing causes left atrial dilatation, atrial fibrillation the type of prosthesis used, and the level of anticoagulation achieved

In terms of over all survival, our experience (Table V) indicates a poorer long term prognosis after mitral or combined valve replacement than after isolated aortic valve replacement Barnhorst and associates[4] also found a lower 4 year survival for patients with mitral valve replacement than for those with aortic valve replacement Starr reported similar survival rates in both groups[1]

The risk of subsequent operations after valve replacement The principal purpose of this review was to evaluate the risk to these patients of either thromboembolism or hemorrhage in association with subsequent, noncardiac operations or invasive diagnostic procedures There were no tested guidelines for the control of anticoagulation during subsequent operations on these patients and this resulted in different approaches to management

The observation that on 25 occasions in patients with isolated aortic valve replacement anticoagulation was discontinued for 3 to 5 days with no thromboembolic complications was noteworthy This was in contrast to the mitral or combined valve replacement group in which two of the 10 patients died of thromboembolic complications when anticoagulation was discontinued None of the nine patients in whom anticoagulation was maintained had thromboembolic complications however, unanticipated hemorrhage did occur in four (Table IV)

Conclusions

Cessation of sodium warfarin for 3 to 5 days to permit surgical hemostasis appears safe in patients with isolated aortic prostheses who require subsequent noncardiac operations Other studies of the interruption of anticoagulants indicate no evidence of the development of a hypercoagulable state

The greater risk of thromboembolism in patients with mitral or combined prosthetic valves requires a more cautious approach to subsequent noncardiac operations Our present protocol is to reverse the warfarin effect just prior to the operation and then to initiate heparin therapy 12 to 24 hours after the procedure on the assumption that adequate hemostasis has occurred Administration of heparin by continuous infusion appears safer than intermittent injection[10] Prior to discharge oral anticoagulation with sodium warfarin is resumed and the heparin therapy is discontinued Preliminary experience with this approach has been encouraging For the individual with an increased risk of thromboembolism such as chronic atrial fibrillation or persistent congestive heart failure it may be safe to perform minor operations such as dental extractions, or other procedures in accessible areas while maintaining anticoagulation[11]

Summary

A total of 111 survivors of prosthetic valve insertion were followed an average of 4 years to assess the risk of thromboembolism or hemorrhage Non-cloth covered ball and/or disc valve prostheses were used and all patients received long term anticoagulant therapy During the follow up period the patients with mitral or combined valve replacement suffered four times more thromboembolic episodes and had a poorer survival rate than the patients with isolated aortic valve replacement The management of anticoagulation and the complications resulting from 44 subsequent noncardiac operations were analyzed Anticoagulation was discontinued before 25 noncardiac operations in patients with isolated aortic valve prostheses and there were no perioperative thromboemboli Ten operations were performed on patients with mitral or combined valve prostheses with cessation of anticoagulation prior to surgery and there were two deaths due to perioperative thromboemboli Unanticipated hemorrhage was encountered in four of nine patients in whom anticoagulation was maintained during surgery Cessation of anticoagulation for 3 to 5 days appears safe in patients with aortic prostheses who require subsequent noncardiac operations The incidence of thromboembolism in patients after mitral or combined valve replacement is high and constitutes a major risk whether or not a subsequent operation is required

REFERENCES

1 Starr A Bonchek L Rahimtoola S H et al Ball valve prostheses Late results (abst) Am J Cardiol 35 710 1975
2 Winter T Q Reis R L Glancy D L et al Current

status of the Starr Edwards cloth covered pro thetic cardiac valves Circulation 45 (Suppl 1) 14 1972.

3. Shean F C Austen W G Buckley M J et al. Survival after Starr Edwards aortic valve replacement Circulation 44 1 1971

4. Barnhorst, [redacted] A Oxman H A Connolly D C., et al. Long term follow up of isolated replacement of the aortic or mitral valve with the Starr Edwards prosthesis Am J Cardiol 35 ^08 19 5

5. Friedli, B Aenchlide N Grondin P et al Thromboembolic complications of heart valve prostheses Am Heart J [redacted] 702 1971

6. Bigelow J C Herr R H Wood J A et al Multiple valve replacement Circulation 38 656 1968

7. Duvoisin G [redacted] Brandenburg R. O and McGoon D C Factors affecting thromboembolism associated with prosthetic heart valves, Circulation 35 (Suppl 1) 70 1967

8. Messmer B J Okies J E Hallman G L. et al Early and late thromboembolic complications after mitral valve replacement J Cardiovasc Surg 13 281 1972

9. Michaels, L. Incidence of thromboembolism after stopping anticoagulant therapy J A M A 215 595 1971

10. Salzman, E W Deykin D Shapiro [redacted] M et al. Management of heparin therapy N Engl J Med 292 1046, 1975

11. McIntyre H Management during dental surgery of patients on anticoagulants Lancet 2 79 1966

Clinical use and toxicity of intravenous lidocaine

A REPORT FROM THE BOSTON COLLABORATIVE DRUG SURVEILLANCE PROGRAM

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Lidocaine hydrochloride is generally considered to be the drug of choice for the treatment of serious ventricular tachyarrhythmias.[1-3] A variety of untoward central nervous system and cardiovascular effects have been attributed to lidocaine[1-6] but there is little information on the incidence of these reactions or on the factors predisposing to them. The present report describes patterns of lidocaine use and toxicity among 750 patients who received the drug intravenously for the treatment of cardiac arrhythmias.

Patients and methods

The scope and operation of the Boston Collaborative Drug Surveillance Program have been described previously.[7-10] Trained nurse monitors stationed on medical wards use standardized self-coding sheets to record information on consecutively admitted patients. Data are collected on patient characteristics, diagnoses, the therapeutic efficacy of all drugs administered, and duration of therapy. When drug treatment is instituted, the prescribing physician is interviewed to determine the therapeutic indications. Reasons for termination of therapy and descriptions of suspected adverse reactions are recorded as well. This report is based on data accumulated since 1966 on 24,778 hospitalized medical patients in nine hospitals in the United States, Canada, Israel, and New Zealand, of whom 750 (3.0 per cent) received intravenous lidocaine.

Results

Patient characteristics. The mean age of the 750 intravenous lidocaine recipients was 64.8 years; 40.1 per cent were aged 70 years or older and 62.1 per cent were men. The primary discharge diagnosis was acute myocardial infarction for 201 patients, ischemic heart disease without documentation of acute infarction for 125, congestive heart failure for 83, and other cardiovascular disorders for 100. A variety of other disorders constitute the remainder of the primary diagnoses (Table I). In all instances intravenous lidocaine was administered for the treatment of cardiac arrhythmias, and in 77 per cent of cases therapy was initiated within 48 hours of admission. Details on lidocaine dosage and on the specific rhythm disorder for which the drug was given were not available for most patients.

Patients receiving lidocaine were commonly administered other cardiovascular agents during hospitalization. These drugs included digitalis glycosides in 463 cases, diuretics (thiazides, mercurials, furosemide, ethacrynic acid, spironolactone) in 452, antiarrhythmics (diphenylhydantoin, beta adrenergic blockers, procainamide, quinidine) in 343, antianginals (nitrates) in 149, antihypertensives (methyldopa, reserpine, guanethidine, hydralazine) in 52, and adrenergic agents (isoproterenol, epinephrine, norepinephrine,

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Table I Primary diagnoses among 750 recipients of lidocaine

Diagnosis		*Per cent of patients*
Cardiovascular disorders		84.0
Acute myocardial infarction	36.8	
Ischemic heart disease without acute infarction	16.7	
Congestive heart failure	11.0	
Rheumatic heart disease	3.1	
Cerebrovascular disease	3.1	
Other	13.3	
Respiratory disease		6.9
Neoplastic disease		2.8
Endocrine disorders		2.4
Gastrointestinal disease		2.2
All other		1.1
	Total	100.0

metaraminol) in 103. Procainamide was administered to recipients of lidocaine in 187 cases and quinidine in 148. Many patients received several cardiovascular drugs.

Of the 750 lidocaine recipients 108 (14.4 per cent) died while in the hospital but physicians responsible for the care of these patients did not judge that lidocaine was the direct cause of any of these deaths.

Adverse reactions. Adverse reactions attributed to intravenous lidocaine were reported in 47 patients (6.3 per cent) and are summarized in Table II. Central nervous system disturbances were by far the most common, being reported in 31 cases. Cardiovascular complications were reported in eight. Four patients had combinations of the two. In 33 of these 47 cases lidocaine therapy was discontinued and not reinstated; in the other 14 the drug was administered again at a later time. Twelve adverse reactions were considered by physicians directly responsible for the care of the patients to be life threatening (Tables II and III). Eight of the patients who suffered life threatening adverse reactions died, but lidocaine was not judged to have been the direct cause of any of the deaths.

Factors influencing the frequency of adverse reactions. Several factors were analyzed to determine their possible association with the frequency of adverse reactions to lidocaine. Lidocaine toxicity occurred early in the course of therapy: 96 per cent of adverse reactions were reported

Table II Adverse reactions attributed to intravenous lidocaine

Reactions	No.
Life threatening	
Central nervous system disturbances	
Somnolence, respiratory depression, or coma	4
Grand mal seizures	2
Cardiovascular complications	
Heart block, cardiac arrest, or hypotension	3
Combinations	
Respiratory depression, tachyarrhythmia, and grand mal seizure	1
Respiratory depression, hypotension, and coma	1
Cheyne-Stokes respiration and hypotension	1
Total	12
Non life threatening	
Central nervous system disturbances (includes confusion, agitation, psychosis, seizures, drowsiness, dysarthria, vertigo, dizziness, tremulousness, visual disturbances, tinnitus, and nausea)	25
Cardiovascular complications (bradycardia, hypotension, or both)	5
Injection site complications (phlebitis)	3
Rash	1
Combinations	1
Total	35
Total with adverse reactions	47

within the first 5 days of therapy and 74 per cent within the first 2 days. In only two cases did an adverse reaction occur after the drug had been given for more than 5 days. Adverse reactions were significantly more frequent among patients with acute myocardial infarction or congestive heart failure and in patients who died (Table IV). Toxicity became increasingly frequent with decreasing body weight (Table IV). Adverse reactions also tended to be more common among elderly individuals and in those who survived long hospitalizations (Table IV). Sex, serum albumin concentration, admission blood urea nitrogen concentration, and coadministration of any of the aforementioned groups of drugs were not significantly related to the frequency of lidocaine toxicity.

Discussion

The present report is based upon prospective monitoring of 750 hospitalized medical patients who received intravenous lidocaine for the treat

Table III Life threatening adverse reactions to lidocaine

Case No	Age (yr)	Sex	Diagnoses	Description of event
1	64	M	Acute myocardial infarction congestive heart failure obstructive pulmonary disease	During the first day of lidocaine infusion the patient had an episode of disorientation and confusion He was found unresponsive the following day The patient recovered 45 to 60 minutes after the drug was discontinued. He died 24 days after the episode
2	56	F	Whipple s disease	The patient received a 50 mg bolus followed by continuous infusion She complained of nausea then became obtunded with depressed respirations. She recovered when the drug was discontinued
3	84	M	Agranulocytosis renal failure	The patient received two 25 mg bolus doses together with continuous lidocaine infusion. He became excessively drowsy and somnolent, but recovered despite continuation of the infusion
4	58	F	Congestive heart failure	During continuous lidocaine infusion (4 mg per minute) the patient became comatose. She recovered 2 hours after the drug was discontinued
5	56	M	Acute myocardial infarction congestive heart failure	During a continuous lidocaine infusion the patient became agitated and confused He recovered when the drug was discontinued. Lidocaine infusion was reinstituted 3 days later On the second day of this course of therapy the patient was given a [illegible] mg bolus *and experienced a grand mal seizure* He died later the same day
6	74	M	Acute myocardial infarction	After 1 hour of lidocaine infusion (? mg per minute) the patient had a grand mal seizure requiring treatment with intravenous diazepam *He died later the same day*
7	85	F	Congestive heart failure	After a 50 mg bolus injection the patient developed bradycardia complete heart block, and cardiac arrest She was successfully resuscitated but died later on the same day

ment of cardiac arrhythmias The age distribution of these individuals (mean 65 years) the frequency of the diagnosis of acute myocardial infarction (27 per cent) the common coadministration of other cardiovascular drugs, and the over all hospital mortality rate (14 per cent) suggest that many of these patients were elderly and seriously ill with cardiovascular disease The observation that lidocaine was given within 48 hours of admission in 77 per cent of cases further indicates that the drug was often administered in urgent clinical situations

Adverse reactions to intravenous lidocaine were reported in 6 per cent of recipients, and in 12 cases (1 6 per cent) the reaction was judged by attending physicians to be life threatening The majority of these adverse reactions were central nervous system (CNS) disturbances They ranged from unwanted CNS depression (i e drowsiness respiratory depression coma) to excess CNS stimulation (i e agitation psychosis seizures) This is consistent with other reports[illegible] Cardiovascular complications such as conduction disturbances bradyarrhythmias or hypotension were reported in eight patients Although several studies suggest that lidocaine does not impair cardiac performance in most patients[illegible] the drug clearly has the potential to cause disturbances of conduction and contractility in susceptible individuals[illegible] Several patients had combinations of untoward CNS and cardiovascular effects Allergic reactions and injection site complications were infrequently reported

We found that adverse reactions to lidocaine

Table III cont'd

Case No	Age (yr)	Sex	Diagnoses	Description of event
8	84	M	Ischemic heart disease congestive heart failure	The patient received lidocaine infusion intermittently for 3 days. He developed a 3 1 heart block and sinus arrest on the third day He recovered when the drug was discontinued The patient died 6 days later
9	64	M	Ischemic heart disease	The patient received a 100 mg bolus followed by continuous lidocaine infusion He suffered a cardiac arrest on the same day Resuscitation was successful but the patient died later that day
10	58	M	Acute myocardial infarction	The patient inadvertently received 1 Gm of intravenous lidocaine within 2 hours. He experienced a grand mal seizure respiratory distress and runs of supraventricular tachycardia He recovered following treatment with intravenous diazepam oxygen and sodium bicarbonate
11	45	M	Ischemic heart disease	The patient received multiple bolus doses (total 700 mg) along with lidocaine infusion He became drowsy then unresponsive with hypotension and respiratory depression He required endotracheal intubation intravenous isoproterenol and sodium bicarbonate The patient recovered from this episode but died 9 days later
[illegible]	[illegible]	F	Ischemic heart disease digitalis toxicity congestive heart failure	On the third day of continuous lidocaine infusion the patient developed Cheyne Stokes respiration and hypotension (80/60 mm Hg) She improved when the infusion rate was reduced The patient died 1 day later

generally occurred early in the course of treatment (within the first 5 days of therapy in 96 per cent of cases and within 2 days in 74 per cent) Adverse reactions were reported more frequently in elderly individuals in those who died and in those with long hospitalizations This probably reflects the tendency of adverse drug reactions to occur more commonly in patients with more serious underlying disease The significant association of adverse lidocaine effects with acute myocardial infarction and congestive heart failure is consistent with pharmacokinetic studies showing that hepatic clearance of lidocaine may be reduced in patients with these diseases [2,2] Since plasma concentrations achieved during lidocaine infusion are inversely proportional to hepatic clearance concentrations in patients with low clearance are more likely to reach potentially toxic levels The finding that adverse effects were more common in patients with low body weight may also reflect the attainment of higher plasma lidocaine concentrations in small individuals with relatively small volumes of distribution

Summary

The clinical use and toxicity of intravenous lidocaine were surveyed in 750 hospitalized medical patients who received the drug for the treatment of cardiac arrhythmias The majority of these patients were older than 60 years and most had diagnoses of cardiovascular disease Lidocaine therapy was started within 48 hours of admission in 77 per cent of cases Adverse reactions to lidocaine were reported in 6 3 per cent of patients but only one in four reactions was considered life threatening Central nervous system disturbances and cardiovascular complications were the most common untoward effects All but two adverse reactions occurred within the first 5 days of treatment Adverse reactions were more common in elderly individuals in those who died and in those with long hospitalizations

Table IV. Factors influencing frequency of adverse reactions to lidocaine

Factor	No. of patients	No. with adverse reactions	
Diagnosis			
Acute myocardial infarction	171	17	(9.9%)
Congestive heart failure	187	16	(8.6%)
Both	40	2	(5.0%)
Neither	352	12	(3.4%)
χ^2 (3 d.f.) = 10.6, p < 0.025			
Survival			
Survived	642	35	(5.5%)
Died	108	12	(11.1%)
χ^2 (1 d.f.) = 4.1, p < 0.05			
Body weight (lb.)†			
Less than 125	111	11	(9.9%)
125 to 149	140	12	(8.6%)
150 to 174	148	9	(6.1%)
175 or more	134	4	(3.0%)
Test for linear trend χ^2 (1 d.f.) = 5.4, p < 0.025			
Age (yr.)			
Less than 50	100	4	(4.0%)
50 to 69	349	19	(5.4%)
70 or older	301	24	(8.0%)
Test for linear trend χ^2 (1 d.f.) = 2.7, p ≃ 0.1			
Length of hospitalization among survivors (days)‡			
Less than 10	224	11	(4.9%)
10 to 19	291	12	(4.1%)
20 or more	125	12	(9.6%)
χ^2 (2 d.f.) = 5.3, 0.05 < p < 0.1			

*Indicates any diagnosis, primary or otherwise.
†Data on body weight not available for 217 patients.
‡Data on length of hospitalization not available for two patients.

Diagnoses of acute myocardial infarction or congestive heart failure and low body weight were also associated with a higher frequency of unwanted effects. Serious adverse reactions to intravenous lidocaine were relatively uncommon. Patients with serious underlying disease or with diminished hepatic clearance of lidocaine appear to be predisposed to adverse effects from this drug.

Hospitals which have participated in the Boston Collaborative Drug Surveillance Program are: Boston, Mass.—Lemuel Shattuck Hospital, Peter Bent Brigham Hospital, Boston City Hospital, Boston Veterans Administration Hospital, Massachusetts General Hospital, and Boston University Hospital; Providence, R. I.—Roger Williams General Hospital; Syracuse, N. Y.—State University Hospital of the Upstate Medical Center; Tucson, Ariz.—Arizona Medical Center; Richmond, Va.—Virginia Commonwealth University Hospital; Canada—St. Joseph's Hospital, London, Ontario; Israel—Hadassah-Hebrew University Hospital, Jerusalem, Beilinson Medical Center, Petah Tiqva, and Asaf Harofe Hospital, Zerifin; New Zealand—Auckland Hospital, Auckland, and Hutt Hospital, Wellington; Scotland—Western Infirmary and Stobhill General Hospital, Glasgow; Italy—Desio Hospital, Milan.

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REFERENCES

1. Bigger, J. T., and Heissenbuttel, R. H.: The use of procaine amide and lidocaine in the treatment of cardiac arrhythmias, Prog. Cardiovasc. Dis. 11:515, 1969.
2. Harrison, D. C., and Alderman, E. L.: The pharmacology and clinical use of lidocaine as an antiarrhythmic drug—1972, Mod. Treat. 9:139, 1972.
3. Collinsworth, K. A., Kalman, S. M., and Harrison, D. C.: The clinical pharmacology of lidocaine as an antiarrhythmic drug, Circulation 50:1217, 1974.
4. Frieden, J.: Antiarrhythmic drugs. Part VII. Lidocaine as an antiarrhythmic agent, Am. Heart J. 70:713, 1965.
5. Nevins, M. A.: Reevaluating the use of lidocaine, Geriatrics 28:48 (Aug.), 1973.
6. Bleifeld, A.: Side effects of antiarrhythmic drugs, Naunyn Schmiedebergs Arch. Pharmakol. 269:282, 1971.
7. Jick, H., Miettinen, O. S., Shapiro, S., Lewis, G. P., Siskind, V., and Slone, D.: Comprehensive drug surveillance, J. A. M. A. 213:1455, 1970.
8. Miller, R. R.: Drug surveillance utilizing epidemiologic methods. A report from the Boston Collaborative Drug Surveillance Program, Am. J. Hosp. Pharm. 30:584, 1973.
9. Miller, R. R.: Comprehensive prospective drug surveillance. A report from the Boston Collaborative Drug Surveillance Program, Pharmaceut. Weekblad 109:461, 1974.
10. Jick, H.: Drugs—remarkably non toxic, N. Engl. J. Med. 291:824, 1974.
11. Foldes, F. F., Molloy, R. E., McNall, P. G., and Koukal, L. R.: Comparison of toxicity of intravenously given local anesthetic agents in man, J. A. M. A. 172:1493, 1960.
12. Jewitt, D. E., Kishon, Y., and Thomas, M.: Lidocaine in the management of arrhythmias after acute myocardial infarction, Lancet 1:266, 1968.
13. Gianelly, R. E., von der Groeben, J. O., Spivack, A. P., and Harrison, D. C.: Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease, N. Engl. J. Med. 277:1215, 1967.
14. Rahimtoola, S. H., Sinno, M. Z., Loeb, H. S., Chuquimia, R., Rosen, K. M., and Gunnar, R. M.: Lidocaine infusion in acute myocardial infarction, Arch. Intern. Med. 128:416, 1971.
15. Grossman, J. I., Cooper, J. A., and Frieden, J.: Cardiovascular effects of infusion of lidocaine on patients with heart disease, Am. J. Cardiol. 24:191, 1969.
16. Lichstein, E., Chadda, K. D., and Gupta, P. K.: Atrioventricular block with lidocaine therapy, Am. J. Cardiol. 31:277, 1973.
17. Jeresaty, R. M., Kahn, A. H., and Landry, A. B.

Sinoatrial arrest due to lidocaine in a patient receiving quinidine, Chest 61 683 197?
8. Lippestad, C T and Forfang K Production of sinus arrest by lignocaine Br Med J 1 537 1971
9 Wood R. A Sinoatrial arrest An interaction between phenytoin and lignocaine Br Med J 1 645 1971
0 Cheng T O and Wadhwa K Sinus standstill following intravenous lidocaine administration J A M A 223 90 1973
1 Marriott, H J L. and Phillips, K Profound hypotension and bradycardia after a single bolus of lidocaine J Electrocardiol. 7 79 1974
12. Parameswaran R Kahn D Monheit R and Goldberg H Sinus bradycardia due to lidocaine Clinical electrophysiologic correlations J Electrocardiol. 7 5 1974
23. Thompson, P D Rowland M., and Melmon K L. The influence of heart failure liver disease and renal failure on the disposition of lidocaine in man AM HEART J 82 417 1971
24 Thompson P D Melmon K L., Richardson J A Cohn K Steinbrunn W Cudihee R Rowland M Lidocaine pharmacokinetics in advanced heart failure liver disease and renal failure in adults Ann Intern Med 78 499 1973
25 Prescott L. F and Nimmo J Plasma lidocaine concentrations during and after prolonged infusions in patients with myocardial infarction in Scott D B and Julian D G editors Lidocaine in the treatment of ventricular arrhythmias, Edinburgh, 1971 E & S Livingstone pp 168-177

Characteristics and coexistence of two forms of ventricular echo phenomena

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The phenomenon of re entry has been demonstrated both experimentally and clinically to occur in most cardiac tissues including the sinus and A V nodes and the His Purkinje system[1-11] Those conditions which are considered requisite for the occurrence of re entry include (1) delayed or asynchronous conduction (2) unidirectional block and (3) recovery of excitability Re entry may result in one or more echo beats or a sustained tachycardia Ventricular echo beats resulting from delayed retrograde A V nodal conduction of premature ventricular beats has been previously described[1-15] More recently it was demonstrated in the human heart that closely coupled premature ventricular beats could also result in ventricular echo beats due to intraventricular re entry involving the His Purkinje system[16] It is the purpose of this report to describe a group of patients in whom single premature ventricular beats resulted in two types of ventricular echo beats In addition a closely coupled premature ventricular beat produced consecutive ventricular echo beats resulting sequentially from intraventricular and A V nodal re entry Both types of re entrant phenomena will be individually characterized and their occurrence and coexistence as a function of delayed retrograde conduction within the A V node and His Purkinje systems will be discussed

Materials and methods

Right heart catheterization was performed in 45 patients with the use of local anesthesia in a nonsedated postabsorptive state The experimental nature of the procedure was explained to all patients and signed consents were obtained Electrode catheters were percutaneously introduced into the antecubital and femoral veins and fluoroscopically positioned in the region of the high right atrium tricuspid valve area, and right ventricular apex for local intracardiac electrogram recordings and/or electrical stimulation[17] Intracardiac electrograms standard electrocardiogram (ECG) Leads I II III and V_1 and time lines generated at 10 and 100 msec were displayed on a multichannel oscilloscope and recorded onto a magnetic tape The records were subsequently reproduced and recorded on a photographic paper at a speed of 150 mm per second Retrograde refractory periods were performed at a basic ventricular cycle length (S_1 S_1 or V_1 V_1) with the ventricular extrastimulus method (S_2 or V_2) The ventricular coupling interval (S_1 S_2 or V_1 V_2) was gradually decreased by 5 to 20 *msec* to the point of ventricular muscle refractoriness For electrical stimulation of the ventricles rectangular impulses of 1 5 msec duration were delivered through an isolation unit at a minimum milliamperage (< 1 ma) which allowed

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reliable ventricular capture All equipment was carefully grounded No incidence of untoward effects occurred

None of the patients had prior evidence of tachyarrhythmias Wolff Parkinson White syndrome or spontaneous atrial or ventricular extra beats Patients with acute myocardial ischemia or electrolyte imbalance were excluded from the study

Definition of terms[8]

The A H interval was measured from the onset of low atrial electrogram (on the His bundle electrogram recording) to the onset of His bundle potential and was taken as an approximation of antegrade A V nodal conduction time Similarly the H V interval which represented antegrade conduction time in the His Purkinje system was measured from the onset of His bundle potential to the earliest recordable ventricular activity on the His bundle electrogram recording or the surface ECG

During retrograde conduction the V A interval representing retrograde His Purkinje and A V nodal conduction time was measured from the corresponding stimulus artifact (S) to the beginning of the low atrial electrogram When retrograde His bundle potential could be recognized during the basic ventricular drive beat (H) or when the His bundle deflection emerged from the ventricular electrogram with the premature ventricular beats (H_2) the retrograde His Purkinje conduction time was measured from the corresponding stimulus artifact to the end of the His bundle potential Likewise H A interval representing retrograde A V nodal conduction time was measured from the end of the His bundle potential to the onset of low atrial electrogram

Results

In a group of 45 patients with intact A V conduction both antegrade and retrograde conduction and refractory period studies were performed but only the results obtained during retrograde refractory period studies will be presented in this report Forty of the 45 patients (group A) demonstrated intact ventriculoatrial (V A) conduction during basic ventricular drive and five of 45 patients (group B) demonstrated no evidence of V A conduction at all ventricular paced rates In the latter group the A V node was the site of unidirectional block

Ventricular echo beats (Ve) resulting from reentry within the A V node This form of ventricular echo phenomenon occurred in 12 of 40 patients in group A and in none of the five patients (group B) who had no V A conduction At predetermined basic ventricular cycle lengths (range 500 to 1 000 msec) the sequence of premature ventricular stimulation was initiated with a relatively late premature beat (S_1 S_2 50 to 100 msec shorter than S_1 S_1) Progressive decreases in S S_2 interval resulted in progressive increases in S_2 A_2 intervals in group A patients Within a certain range of S_1 S_2 intervals (range 600 to 330 msec) and S_2 A_2 intervals (range 220 to 550 msec) another ventricular beat (Ve) appeared in 12 of the group A patients (Fig 1) In most patients the retrograde His bundle potential (H_2) for these relatively late premature beats was obscured within the ventricular electrogram and for the reasons listed below it can be reasonably inferred that the Ve resulted from A V nodal reentry and henceforth will be referred to as Ve AVN

1 Ve AVN was preceded by retrograde activation of the atria i e a low to high atrial activation sequence in contrast to the sequence of atrial activation during the sinus beats which was from the high to low atrium

2 Ve AVN was always preceded by an H V interval equal to that of sinus beats

3 The QRS morphology of Ve AVN was the same as that of sinus beats

4 The occurrence of Ve AVN was dependent upon achievement of critical S_2 A or H_2 A delays (see below)

5 Ve AVN did not occur when S_2 retrogradely blocked in the A V node but reappeared when V_2 A conduction resumed at closer S_1 S_2 coupling intervals (phenomenon of retrograde gaps)[3]

6 Ve AVN was never observed in the five patients who had no V A conduction (group B)

7 Ve AVN disappeared at closer V V_2 intervals because the latter resulted in longer S_2 H_2 delays which permitted recovery of A V node and prevented attainment of the requisite H A_2 delay

It is important to note that Ve AVN occurred at relatively long S S_2 intervals and prior to the emergence of H from the V_2 electrogram Therefore direct measurements of the degree of retro

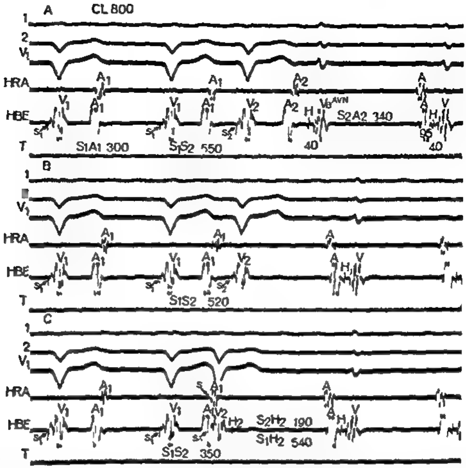


Fig 1 Ventricular echo (re entry A V node) Tracings in each panel are ECG Leads I II V high right atrial electrogram (HRA) His bundle electrogram (HBE) and time lines (T) at 10 and 100 msec S denotes stimulus artifact The same abbreviations are used in subsequent tracings The basic ventricular cycle length ($S_1 S_1$) is 800 msec in all panels and $S_1 A_1$ measures 300 msec In panel A a premature ventricular beat (V) coupled at an $S_1 S$ interval of 550 msec conducts retrogradely with an S A interval of 340 msec A is followed by another ventricular beat (Ve AVN) having the same QRS morphology and H V interval as the sinus beat which follows Note the low to high atrial activation sequence during ventricular pacing whereas a high to low sequence is recorded during sinus beats At a closer coupling interval (panel B) S retrogradely blocks prior to emergence of H from the V_2 electrogram Panel C shows emergence of H from the V electrogram at closer $S_1 S$ interval and H is not followed by atrial activation (retrograde A V nodal block) Retrograde block of S in the A V node is not associated with Ve AVN The amplitude of QRS complexes has been deliberately reduced to avoid excessive levels during ventricular pacing on the tape recorder

grade A V nodal (H A interval) delays were not always available However following the emergence of H_2 from V_2 at closer coupling intervals it could be documented that this form of ventricular echo beat was dependent upon H A delays rather than S H delays Furthermore in nine of 40 patients the retrograde His bundle potential was identifiable during the basic ventricular drive and it could be directly determined that with late premature beats (i e, with $S_1 S_2$ of 450 msec or longer) increases in S A intervals were entirely the result of increases in H A_2 intervals and not due to delays below the bundle of His (i e S H_2 interval)

The degree of retrograde A V nodal delay was up to a point inversely related to the $V_1 V_2$ interval At very short V_1 V intervals premature ventricular beats (V) encountered retrograde conduction delay within the His Purkinje system causing an increase in the S H intervals The relatively later arrival of the V impulse into the A V node resulted in a decrease in the H A_2 interval Therefore for a given S_1 S interval the resulting S_1 H interval was lesser or greater compared to the S H_2 interval resulting from longer or shorter S S intervals

In the remaining 28 patients with intact V A conduction Ve AVN did not occur despite premature ventricular stimulation at comparable $V_1 V_2$ intervals and the attainment of comparable V A_2 interval delays Thus the frequency of Ve AVN was found to be 30 per cent (12 of 40) in patients with intact V A conduction

Ventricular echo beats resulting from re entry

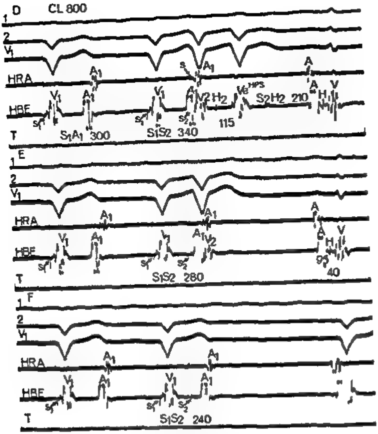


Fig 2 Ventricular echo (re-entry HPS) This figure demonstrates further continuation of the sequence of ventricular premature stimulation at progressively decreasing coupling intervals in the same patient and at the same basic ventricular cycle length as Fig 1 In Panel D S_2 conducts to the His bundle with an S_2H_2 interval of 210 msec but is blocked in the *A V* node (no A_2) V_2 is followed by another ventricular beat (*Ve HPS*) which has similar QRS morphology and axis orientation as V_2, and is preceded by H V interval of 115 msec In panel *E* at a closer S_1S_2 interval of 280 msec *S_2 blocks below the bundle of His and Ve HPS* does not occur Panel *F* simply shows the S_1S_2 interval at which S_2 fails to evoke a ventricular response

within the His Purkinje system Within a given range of short V V_1 intervals all 45 patients demonstrated retrograde conduction delay within the HPS which was reflected in emergence of H_2 from the V electrogram

In 20 of 45 patients retrograde conduction delay within the HPS was associated with another type of ventricular echo beat hereafter referred to as Ve HPS (Fig 2) and having the following characteristics

1 Ve HPS when present always occurred after H emerged from the V electrogram

2 Ve HPS occurred within a narrow range of close V V intervals (210 to 350 msec)

3 The occurrence of Ve HPS was dependent upon S H_2 delays (range 120 to 350 msec) and was independent of H_2 A delays

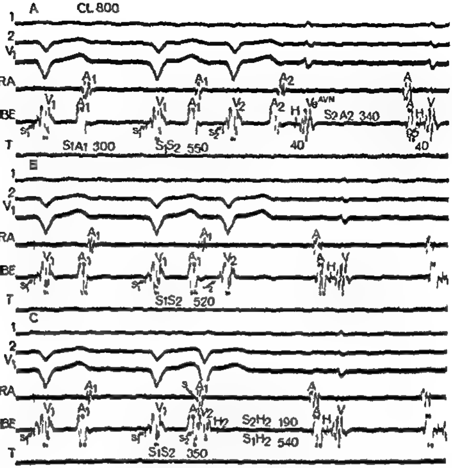
4 Ve HPS did not occur when S_2 retrogradely blocked below the bundle of His and reappeared when S H_1 conduction resumed at closer ventricular coupling intervals (the phenomenon of retrograde gaps) *

5 Ve HPS persisted when S_1 blocked above the bundle of His (A V node) and was also seen in two of five patients who had no V A conduction across the A V node

6 When the right ventricular apex was site of stimulation the QRS morphology and axis orientation of Ve HPS was similar to V_2 (left bundle branch block pattern)

7 Ve HPS did not occur in patients having a pre existing right bundle branch block pattern (see below)

The aforementioned characteristics of Ve HPS strongly suggest that re entry of V was via a macro re entrant circuit utilizing the bundle branches and bundle of His [15] It is postulated that within the critical range of coupling intervals S



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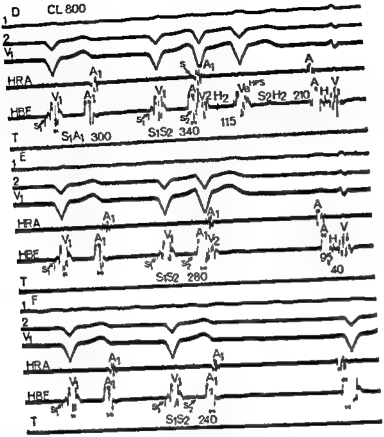

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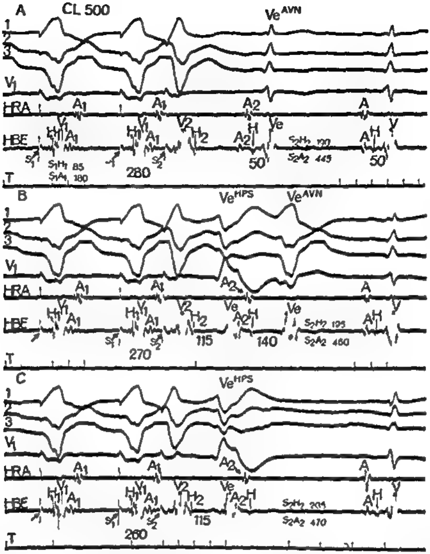


Fig 3 Dual re entry (A V node and HPS) The basic ventricular CL is 500 msec in all panels The retrograde His bundle potential is recognizable during the basic drive (H_1) At an $S_1 S_2$ interval of 260 msec (Panel *A*) S_2 conducts to the atria with an $S_2 H$ interval of 190 (H_2 follows V_2) and an $H_2 A$ interval of 2[illegible] msec and a *Ve AVN* follows Compare the atrial activation sequence preceding *Ve AVN* with sinus beats Panel *B* shows that at closer $S_1 S_2$ interval and longer $S_2 H_2$ interval (compared to panel *A*) V_2 is followed by another ventricular beat labeled *Ve HPS* *Ve HPS* precedes A_2 and is preceded by an H V interval of 115 msec The QRS morphology of *Ve HPS* (RBBB) is compatible with activation from the left ventricular (see text for details) The *Ve HPS* is followed by another ventricular beat (*Ve AVN*) which is preceded by similar $H_2 A_2$ and A H intervals as in panel *A* but a longer H V interval (140 msec) The QRS morphology of *Ve AVN* (LBBB pattern) suggests that the *Ve HPS* after activating the ventricles failed to engage the right bundle branch retrogradely and the latter was utilized by the A V nodal re entrant impulse Panel *C* shows essentially the same events as panel *B* except that the A V nodal re entrant impulse antegradely blocks below the bundle of His This is not unexpected if one considers that the H V interval in panel *B* represents markedly prolonged conduction time in the HPS

which is delivered to the right ventricle is retrogradely blocked within the right bundle branch The later arrival of S_2 within the left bundle branch permitted retrograde conduction back to the bundle of His, after which if the right bundle branch and/or ventricular muscle recovered sufficiently, antegrade conduction and re excitation of the right ventricle was possible This route of re entry also explains the similarities between the QRS morphology and axis orientation of Ve HPS and that of V The fact that Ve HPS were preceded by H V intervals considerably longer than those of sinus beats indicates that the re entrant impulse was antegradely conducted during the incomplete recovery phase of the right bundle branch–Purkinje system and/or ventricular muscle These observations also suggest that local re entry occurring near the site of stimulation is an unlikely mechanism of Ve HPS in this group of patients

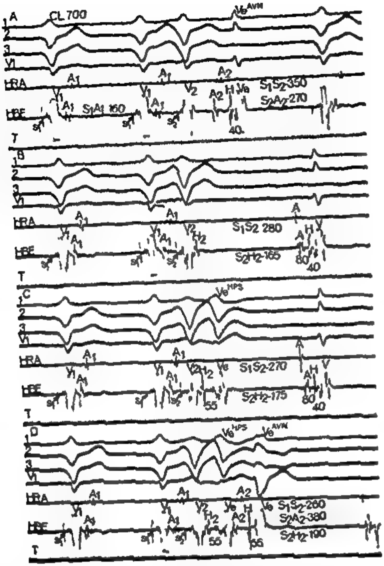
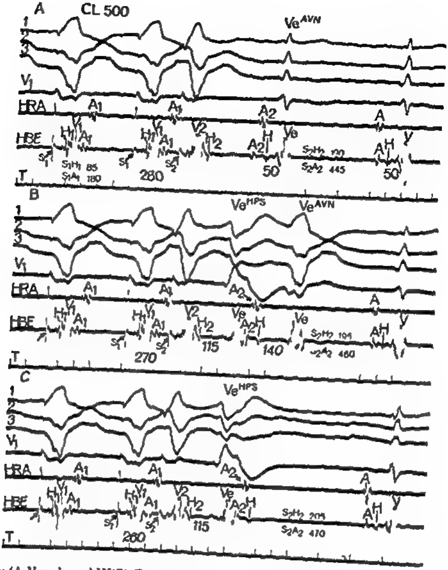


Fig 4 Dual re-entry (A V node and HPS) The basic ventricular drive rate is 00 msec Panel *A* shows a *Ve AVN* resulting from an S_2A_2 *of 270 msec* at a ventricular coupling interval of 350 msec In panel *B* S_2 blocks retrogradely in the A V node and *Ve AVN* does not occur At a closer coupling interval of 2 0 msec (panel *C*) S_2 still blocks retrogradely in the A V node but is associated with longer S_2H_2 interval (175 msec) which results in *Ve HPS* Note the similarity between the QRS complexes of V_2 and *Ve HPS* Panel *D* shows a *Ve HPS* occurring at an S_1S_2 interval of 60 msec and an S_2H_2 interval of 190 msec The longer [illegible] H interval in panel *D* of 450 msec (not labeled) compared to panels *B and C* (445 msec) results in resumption of retrograde A V nodal conduction and *Ve AVN* (a retrograde gap phenomenon) The *Ve AVN* in panel *D* has a left bundle branch block pattern and *longer* [illegible] *V interval compared to panel A (see text for details)*

In two patients Ve HPS had a QRS morphology of right bundle branch block pattern indicating excitation starting from the left ventricle (Fig 3) This is consistent with re entry by reciprocation within the left bundle branch system or perhaps V_2 was retrogradely conducted by the right bundle branch and then antegradely activated the ventricles by the left bundle branch The foregoing hypothesis is based upon the assumption that in some patients retrograde refractoriness of the left bundle branch exceeds that of the right bundle branch In two patients Ve HPS was preceded by H V intervals that were shorter than H V intervals of sinus beats Under these settings depending upon the QRS morphology of Ve HPS one may postulate reciprocation



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appeared to be dependent upon retrograde conduction delay in the A V node and Ve HPS upon conduction delay within the HPS

2 *Unidirectional block* [1 1 2] The completion of a re entrant phenomenon is difficult to envision without accepting the concept of unidirectional block On the assumption that the proposed mechanism of Ve HPS is most likely it would appear that a *retrograde block in the right* bundle branch system was required for manifestation of Ve HPS In all probability similar mechanism was operative during Ve AVN however documentation of unidirectional block during A V nodal re entrant process is more difficult to obtain

3 *Recovery of excitability* It is obvious that recovery of excitability must occur before a tissue can be re excited which is the case during manifest form of any re entry The concealed form of re entry probably occurs more frequently than is generally realized and may be the case in some patients in this series in whom significant degrees of conduction delays were achieved but Ve AVN and/or Ve HPS did not occur

4 **Further considerations** Finally it must be pointed out that even if all the above conditions are met a critical balance between conduction and refractoriness must exist within the various limbs of a re entrant circuit for effective propagation of a re entrant impulse

In the present series Ve AVN occurred only in those patients in whom the requisite $V_2 A_2$ delays were the result of conduction delay in the A V node (i e H A delay)

In 12 of 40 patients in group A requisite $V_2 A_2$ delays were achieved but Ve AVN did not occur It became apparent in these patients that at close S S intervals when H emerged from the V electrogram the long $V_2 A_2$ intervals resulted primarily from S H delays The H A delays were of relatively short duration i e < 50 msec Consequently requisite retrograde A V nodal delay for re entry was never achieved It is also interesting to note that in these 12 patients S never retrogradely blocked in the A V node Likewise in the five patients who had no V A conduction Ve AVN did not occur These observations suggest that lack of sufficient conduction delay and absence of conduction across the A V node will not favor the occurrence of manifest A V nodal re entrant phenomenon In the remaining 16 patients who had no Ve AVN the magnitude of $H_2 A_2$ delays was the same as in those patients who did have re entry For these patients one may postulate that factors other than conduction delay as mentioned above were not operative

The Ve HPS was seen relatively more frequently in this series of patients i e 20 of 45 This is particularly striking if one considers that 10 of 45 patients in this series had pre existing complete right bundle branch block pattern a condition which does not favor Ve HPS (one of ten patients) This means that in the absence of complete right bundle branch block Ve HPS occurred in 19 of 35 patients or 54 per cent whereas Ve AVN occurred in 12 of 45 patients (27 per cent) If the mechanism and route of re entry of Ve HPS is the one suggested above (see results) then one will not expect to see Ve HPS in patients with antegrade right bundle branch block or retrograde left bundle branch block when the premature ventricular beat originates from the right ventricle Three patients in this series had pre existing left bundle branch block pattern two of which were rate related The Ve HPS was seen in the two patients with rate related left bundle branch block pattern

Both Ve AVN and Ve HPS in this study were seen generally as one and occasionally as two consecutive beats and the process terminated spontaneously The lack of sustained re entry may relate to the fact that the critical balance of conduction and refractoriness between the various limbs of the re entrant circuit which is necessary to sustain any form of re entry was not attained in these patients

The coexistence of dual re entry i e A V nodal and His Purkinje at the same time can produce complex ECG patterns and may mimic multiple multifocal ventricular beats Results of this study indicate that some of these ventricular beats may be of A V nodal re entrant origin This of course will be difficult to determine from the surface ECG The QRS morphology and the axis orientation of Ve AVN depend upon the influence and the degree of penetration of the HPS by the preceding Ve HPS

For example if the Ve HPS after activating the ventricular muscle fails to retrogradely penetrate the left bundle branch the oncoming A V nodal re entrant impulse will find the right bundle

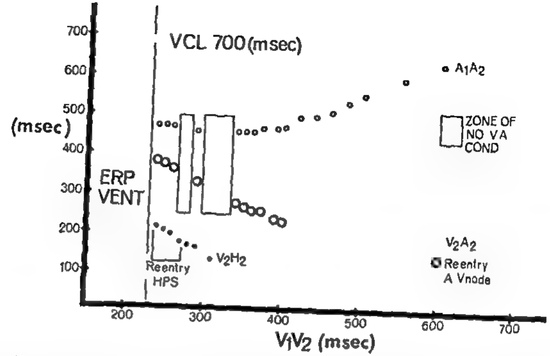

Fig 5 Dual re entry (A V node and HPS) The figure is a graphic display of the sequence of events during premature ventricular stimulation and depicts some of the typical aspects of dual re entry (same patient and cycle length as Fig 4) The coupling intervals (abscissa) are plotted against V_2H_2, V_2A_2, and A_1A_2 intervals (ordinate) Note progressive increase in V A intervals as V_1V_2 intervals are decreased A V nodal re entrant echo beats (larger circles) appeared at V_1V_2 intervals of 400 msec or less and V_2A_2 of 230 msec or greater prior to the emergence of H_2 from V_2 At V_1V_2 of 340 msec V_2 blocks retrogradely (zone of no V A conduction) and Ve AVN is abolished The H_2 emerges from V_2 (larger dots) at a V_1V_2 of around 320 msec which localizes the site of retrograde block to the A V node At closer V_1V_2 interval of 270 msec when V_2H_2 interval is of sufficient magnitude Ve HPS appears (bracketed) while the retrograde A V nodal block persists (see also Fig 4) At closer coupling intervals V A conduction resumes and V_2 results in dual re entry up to the point of ventricular muscle refractoriness.

within the right or left bundle branch

Dual re entry (Ve AVN and Ve HPS) In nine patients from group A both Ve AVN and Ve HPS were observed during the sequence of premature ventricular stimulation In all nine patients Ve AVN was initiated at longer ventricular coupling intervals (S_1S_2 range 330 to 580 msec Figs 1 3 4 and 5) and Ve HPS was initiated at shorter coupling intervals (S_1S_2 range, 270 340 Figs 2 to 5) In five of these nine patients both forms of re entrant ventricular echo beats resulted from a single premature ventricular impulse (Figs 3 to 5)

The zone of S_1S_2 intervals at which both forms of ventricular echo beats resulted from a single S_2 impulse were quite narrow (30 to 90 msec range of S_1S_2 200 to 300 msec)

The QRS morphology of Ve AVN was always aberrant when a Ve HPS preceded it The aberrant QRS morphology of the Ve AVN was either of a left or right bundle branch block type (Figs 3 and 4)

Discussion

The results of this study demonstrate that at least two different types of ventricular echo beats may result from premature stimulation of the right ventricle Relatively late premature ventricular beats produce only Ve AVN whereas closer premature beats may produce either Ve AVN or Ve HPS or both The occurrence of one or the other type of ventricular echo beat was directly related to the degree of retrograde conduction delay achieved in either the A V node or the HPS Manifestation of reentry in the form of echo beats depend upon the interplay of many factors The precise role of the various factors involved in the re entrant process is far from clear However some of the more accepted concepts may be briefly mentioned in relation to the observations made during the present study

1 Conduction delay The association of conduction delays and re entrant phenomena a frequently observed relationship was consistently seen during the present study The Ve AVN

orrelations between the spread of ventricular ctivation and map patterns of measured and ifference maps

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t has been reported by Taccardi Spach and associates,[3] and Boineau and associates that a body surface isopotential map (measured map) shows special map patterns such as saddle niche and so on depending upon the propagation process of ventricular activation in the heart The appearance of these map patterns was first postulated by Taccardi to be a phenomenon that could not be explained by the single fixed locational dipole hypothesis[7] Later this was experimentally supported and confirmed by Horan and associates[8]

In a previous report Toyoshima and associates observed that a *component of potentials which* cannot be explained on the basis of the single fixed locational dipole hypothesis was presented in measured and difference maps especially in the latter which were obtained by delineating the difference in potential between measured and simulated maps A simulated map is one obtained by mathematical calculation of the potential at every lead point of the thoracic surface through the use of the equation proposed by the authors It was also observed that the difference map was highly suggestive of the spread of ventricular activation at each instant

In the above experiments however a clear cut conclusion could not be obtained mainly because the effect of the electric conductivity on the potential distribution might be different between an inhomogeneous human torso and its homogeneous torso model and the actual process of ventricular activation could not be obtained with a human heart

The present experiments were performed on canine hearts in order to study further the relationship between the spread of ventricular activation and the map patterns of measured and difference maps

Methods

1 **Measurements of lead vectors of 85 unipolar leads and of the three component leads of the corrected orthogonal lead system designed by the author** The cylindrical torso model used for the present experiments was of acrylic resin its inside diameter was 18 cm and its height was 44 cm Silver electrodes 1 5 mm in diameter were implanted through the cylinder wall at specific points The points selected were the 168 intersections formed by seven horizontal lines drawn at 2 5 cm intervals beginning from 8 cm below the ridge of the cylinder and the 24 longitudinal lines which equally divided the circumference of the cylinder Thus the longitudinal and circumferential distances between each two adjacent points were both 2 5 cm In addition four electrodes were implanted near the top and two more near the bottom of the cylinder to serve as the limb leads and Y lead of the corrected orthogonal lead system

To examine the orthogonality of the lead vectors of three component leads X Y and Z these were experimentally obtained by placing a unit of artificial electric dipoles at each of 27 representative points on a cubic area 5 cm [3] which covered the entire ventricular mass of the canine heart The results are shown in Table I

The lead points of the unipolar lead electrocar

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branch more refractory since it was the last one to be activated and descend along the left bundle branch with resultant QRS complex displaying right bundle branch block pattern On the other hand, if Ve HPS does penetrate the left bundle branch retrogradely, then the oncoming A V nodal re entrant impulse may propagate along the right bundle branch and the resulting QRS complex will have a left bundle branch block pattern (Fig 4) Regardless of the origin of Ve HPS at times both bundle branches and/or the Purkinje network may be effectively refractory to the A V nodal re entrant impulse which may then display a block within the HPS (Fig 3)

Summary

During the scanning of paced basic ventricular cycle lengths ($V_1 V_1$) with extrastimulus method (V_2) two forms of ventricular echo phenomena (Ve) were recognized The Ve resulting from A V nodal re entry (VeAVN) occurred in 12 of 45 patients, from re entry in the His Purkinje system (Ve HPS) in 20 of 45 patients and simultaneous dual re entry (Ve AVN and Ve HPS) occurred in five of 45 patients The Ve AVN (1) appeared at longer $V_1 V_2$ intervals (2) was dependent on retrograde A V nodal conduction delay (3) had normal QRS complexes and H V intervals, and (4) did not occur when V_2 blocked in the A V node (5) Ve AVN had aberrant QRS complexes when preceded by Ve HPS The Ve HPS (1) appeared at shorter $V_1 V_2$ intervals (2) was dependent upon retrograde conduction delay in the HPS (3) its QRS morphology and axis orientation resembled V i e, left bundle branch block pattern, when right ventricular apex was the site of stimulation, (4) persisted when V_2 blocked in the A V node and was abolished when V_2 blocked below the bundle of His and (5) rarely occurred in patients with pre existing right bundle branch block It is concluded that (1) at least two forms of Ve can result from induced premature ventricular beats (2) Ve HPS is more common than Ve AVN in the presence of normal QRS complexes and (3) coexistence of Ve AVN and Ve HPS can give rise to complex ECG pattern mimicking multiple multifocal premature ventricular beats

REFERENCES

1 Schmitt F O and Erlanger J Directional differences in the conduction of the impulse through heart muscle and their possible relation to extrasystolic and fibrill contractions Am J Physiol 87 326 1928 29
2 Scherf D and Schott A Extrasystoles and a. arrhythmias New York 1953 Grune & Stratton Inc
3 Han J Malazzi A M and Moe G K Sinoatrial reciprocation in the isolated rabbit heart Circ Res 22 355 1968
4 Paulay K L Varghese P J and Damato A N Sinus node reentry An in vivo demonstration in the dog Circ Res 32 455 1973
5 Paulay K L Varghese P J and Damato A N Atrial rhythms in response to an early atrial premature depolarization in man Am Heart J 85 323 1973
6 Janse M J VanCapelle F J L Freud G E and Durrer D Circus movement within the A V node as a basis for supraventricular tachycardia as shown by multiple microelectrode recording in the isolated rabbit heart Circ Res 28 403 1971
7 Mendez C and Moe G K Demonstration of a dual A V nodal conduction system in the isolated rabbit heart Circ Res 19 378 1966
8 Goldreyer B N and Bigger J T Jr The site of reentry in paroxysmal supraventricular tachycardia Circulation 43 15 1971
9 Bailey J C Anderson G J and Fisch C Reentry within the isolated canine bundle of His A possible mechanism for reciprocal rhythm Am J Cardiol 31 117 1973
10 Cranefield P F Klein H O and Hoffman B F Conduction of cardiac impulse delay block and one-way block in depressed Purkinje fibers Circ Res 28 199 1971
11 Wit A L, Hoffman B F and Cranefield P F Slow conduction and reentry in the ventricular conducting system Circ Res 30 1 1972
12 Rosenblueth A Ventricular echoes Am J Physiol 195 53 1958
13 Mignone R J and Wallace A G Ventricular echoes Evidence for dissociation of conduction and reentry within the A V node Circ Res 19 638 1966
14 Mendez C Han J Garcia de Jalon P D and Moe G K Some characteristics of ventricular echoes, Circ Res 16 562 1972
15 Goldreyer B N and Bigger T J Jr Ventriculoatrial conduction in man Circulation 41 939 1970
16 Akhtar M Damato A N Batsford W P Ruskin J N Ogunkelu J B and Vargas G Demonstration of re entry within the His Purkinje system in man Circulation 50 1150 1974
17 Scherlag B J Lau S H Helfant R H Berkowitz W D Stein E and Damato A N Catheter technique for recording His bundle activity in man Circulation 39 13 1969
18 Akhtar M Damato A N Caracta A R Batsford W P and Lau S H The gap phenomenon during retrograde conduction in man Circulation 49 811 1974
19 Goldreyer B N and Damato A N The essential role of A V conduction delay in the initiation of paroxysmal supraventricular tachycardia in man Circulation 43 15 1971
20 Mendez C and Moe G K Demonstration of dual A V nodal conduction system in the isolated rabbit heart Circ Res 19 378 1966
21 Watanabe Y and Dreifus L S Inhomogeneous conduction in the A V node Am Heart J 70 505 1965

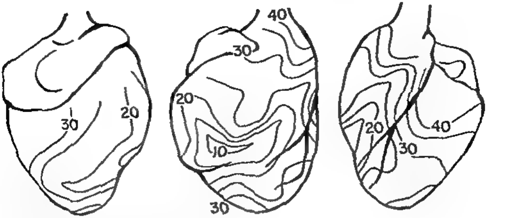


Fig 2 Isochronic maps showing the epicardial sequence of the ventricular activation in QRS duration From left to right right lateral frontal and left lateral views The time interval of the isochronic lines 5 msec numerical values indicate the respective arrival times of the activation front

and 30 C and its millimolar constitution was slightly modified as follows NaCl 137 KCl 2 7 MgCl 0 5 CaCl 2 7 NaH PO 1 8 NaHCO 22.5 and dextrose 5 5 pH at about 7 2

Then the canine heart was immersed in the cylindrical torso model filled with the Tyrode s solution and positioned as described with the aid of supporting apparatus so as to assume the position analogous to that of the heart in the human thorax

A four-channel data recorder (Teac Corporation R 100) with magnetic tape (Teac Corporation ¼ DT 250 1800 PR) was used to record simultaneously two unipolar lead ECG s from each pair of adjacent lead points on the torso surface and a direct bipolar lead ECG from two fixed lead points on the ventricular wall which served as a time reference This procedure was repeated 43 times until all 85 unipolar lead ECG s were recorded (tape speed 19 cm per second) Amplification was performed by a four channel preamplifier (Nihon Kohden Kogyo Co Ltd RB 5) at a time constant of 0 3 second and cut off frequency of low pass filter at 300 Hz

When the 85 recordings were finished the three component lead ECG s of the corrected orthogonal lead system were also taped together with the same time reference ECG under the same recording conditions

Next the heart was moved to the liquid surface and direct unipolar and simultaneous contiguous bipolar lead ECG s were recorded at 20 cm per second from 40 to 50 points of the epicardium together with the same time reference ECG (direct writing electromagnetic oscillograph Yokogawa Electric Works Ltd LMO 62 oscillograph paper Oriental Photo Ind Co Ltd C 123) The contiguous bipolar electrodes were insulated platinum wires (0 2 mm in diameter) and the interpolar distance of the electrodes was 0 5 mm

3 Delineation of isochronic and torso surface isopotential maps An isochronic map expressing the epicardial sequence of the ventricular activation of the canine heart was obtained by plotting the points showing the same time of activation arrival at the epicardial side This arrival time was determined by measuring the time from the onset of ventricular activation to the peak of the main deflection of each direct contiguous bipolar lead ECG also referring to the steepest part of intrinsic deflection of each direct unipolar lead ECG The earliest onset among QRS deflections of direct unipolar lead ECG s was conventionally assumed to be the actual onset of ventricular activation

The taped 85 unipolar lead ECG s were reproduced transmitted to an A/D converter and mapped by a minicomputer as explained in previous papers The sampling rate was about 2 600 samples per second for each lead Synchronization of 43 pairs of unipolar lead ECG s was performed by using the steepest point of downward deflection of the time reference ECG The averaged potentials of four selected points in a flat portion of TP interval in each unipolar lead ECG was assumed to be zero potential or the potential of Wilson s central terminal in the

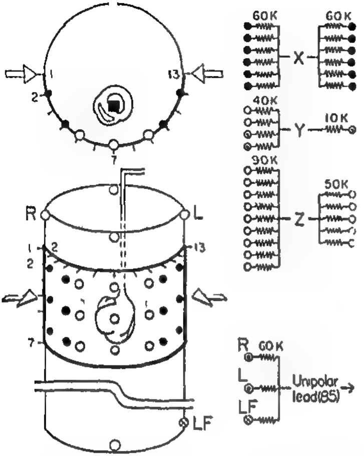


Fig. 1 The locational relationship between the cylindrical torso model and the canine heart undergoing artificial perfusion is seen at the lower left. A transverse section of the cylinder containing the heart is shown above, with a black square representing the approximate place where the artificial dipole or the ventricular center was situated. The unipolar lead electrodes were respectively implanted in the area enclosed by the heavy line (lower inset) at the intersections of seven horizontal and 13 longitudinal lines. A part of the lead points which coincided with those for the corrected orthogonal lead system is shown in the lower one. On the right are shown the networks of the corrected orthogonal lead system used and of Wilson's central terminal.

Table I The lead vectors of X, Y, and Z leads of the corrected orthogonal lead system used in this experiment

	X component	Y component	Z component	$\sqrt{X^2+Y^2+Z^2}$
Lead X	118	[illegible]	3	118
	116.2 ± 16.4	4.4 ± 4.[illegible]	5.0 ± 12.2	117.1 ± 16.3
Lead Y	1	108	3	10[illegible]
	1.0 ± 0.3	107.2 ± 0.3	2.8 ± 0.[illegible]	10[illegible] ± 1.0
Lead Z	3	0	100	100
	3.4 ± 8.5	2.4 ± 11.1	98.3 ± 11.1	99.3 ± 14.1

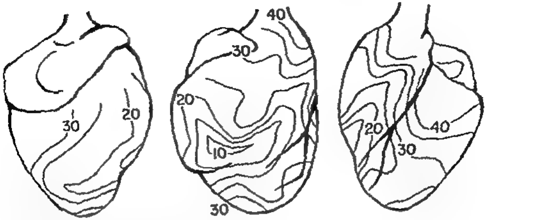
The upper row in each column shows the lead vector values obtained when the artificial dipole was situated where the ventricular center was placed; the lower one indicates the mean and standard deviation of [illegible] lead vector values obtained when the artificial dipole was placed at [illegible] cube of 27 representative points along a cubic area [illegible] cm which covered the entire ventricular mass of the heart (the eight corners, middle points of the 12 edges, centers of the six faces and the center of the cube itself).

diograms (ECG's) used for the delineation of the torso surface isopotential map were 85 lead points out of 91 within the rectangular area indicated by the thick solid line and covering half the cylinder circumference as shown in Fig. 1. Six points of bilateral areas corresponding to the shoulder joints of the human torso were excluded from measurement for mathematical reasons in computer programming. Part of the lead points coinciding with those of the corrected orthogonal lead system are illustrated in Fig. 1.

The positioning of the heart in the cylinder cavity was nearly identical to the locational relationship described in a previous paper for a human torso model in which the ratio of the distance from the ventricular center of the heart to the anterior chest wall to the depth of the thorax was 30 per cent. In the present experiment the ventricular center was situated on the level of the fourth (middle) horizontal line at a point 4 cm anterior from the exact center of the cylinder. The distance from here to the closest point on the cylinder inside surface was 27 per cent of the cylinder diameter itself.

The electric dipole unit equipped with three rectangular electric axes was placed at the point assumed to be the ventricular center so that the axial orientations coincided with those of the three standard axes of the cylindrical torso. The cylinder was then filled with 0.1 per cent NaCl solution and the lead vectors of the 85 unipolar leads and those of the three component leads of the corrected orthogonal lead system were obtained in the same way as described in the previous paper.

2. Experiments on canine hearts undergoing artificial perfusion. The experimental animals were mongrel dogs weighing 7 to 10 kilograms. The dogs were anesthetized by intravenous administration of pentobarbital sodium (30 mg per kilogram) and given an intravenous injection of 5,000 units of heparin sodium. The heart was then excised and Langendorff's preparation of the heart undergoing perfusion with oxygenated Tyrode's solution was made. The temperature of the Tyrode's solution was kept between 28° C



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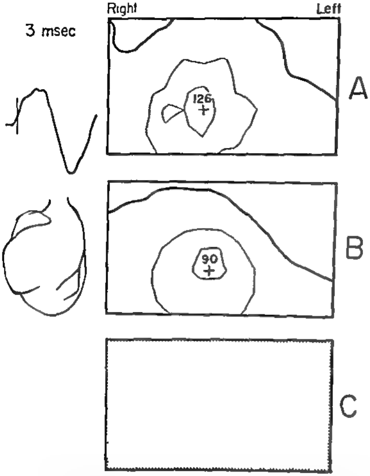

Fig 3 *A* Measured *B* simulated *C* difference maps obtained at 3 msec after the onset of ventricular activation The heavy solid line in each map plots the points where the electric potential is equal to that of Wilson s central terminal in the resting stage The thin lines represent equipotential in 40 μV gradations The dotted area in the difference map indicates neutral area with difference in potential of less than $\pm$ 40 μV Upper left Z lead ECG Lower left frontal view of the heart showing the epicardial spread of the ventricular activation The activation front has not as yet reached the epicardial side

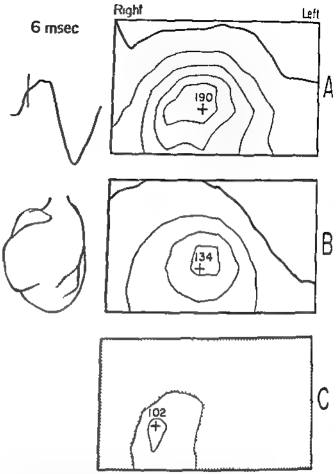

Fig 4 Three maps obtained 6 msec after the onset of ventricular activation Thin lines in the difference map (*C*) represent equidifference lines drawn in 40 μV gradations The map patterns of the measured (*A*) and simulated (*B*) maps were similar except for a positive area appearing in the difference map See the legend of Fig 3 for additional explanation

resting stage Thus torso surface isopotential maps (measured maps) were obtained every 1 5 (or 3) msec throughout the entire time course of ventricular depolarization Equipotential lines were delineated in 40 μV gradations

Simulated and difference maps were also delineated every 1 5 (or 3) msec by the same methods as described in the previous paper For a simulated map the magnitude and direction of the resultant electromotive force of the ventricle at each instant of QRS duration were determined from the potential differences measured every 1 5 (or 3) msec with the three component (X Y and Z) lead ECG s of the corrected orthogonal lead system They were assumed to express the electrical moment of the fixed locational electric dipole hypothetically placed to the ventricular center at the same instant For the determination of the potential differences of these three component leads the potential differences of five QRS complexes in each of X Y and Z leads were averaged Then the potential values at 85 lead points that should be produced by this electric dipole were calculated from the quantity of each lead vector of 85 unipolar leads as well as that of the three component leads of the corrected orthogonal lead system and from each potential difference measured on these three component lead ECG s by applying the equation described in the previous paper Based on the potentials of the 85 lead points thus obtained equipotential lines were delineated in 40 μV gradations (simulated map)

The difference in potential value between

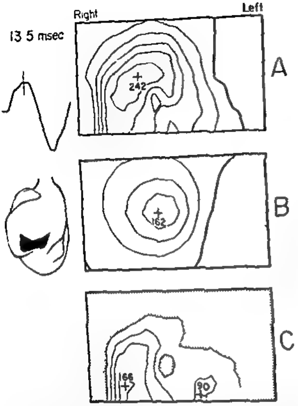

Fig 5 Three maps obtained at 13.5 msec after the onset of ventricular activation In the measured map (*A*) bending of equipotential lines toward the maximum is seen at the mid lower region In the simulated map (*B*) equipotential lines are almost concentric In the difference map (*C*) an extensive positive area containing a localized neutral area is seen As shown by the shaded area on the epicardial surface the activation front has already arrived at the epicardial side resulting in the epicardial breakthrough

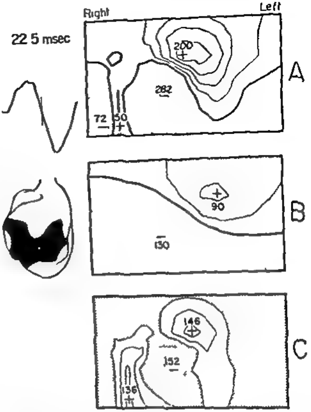

Fig 6 Three maps obtained at 22.5 msec after the onset of ventricular activation The dotted lines in the measured (*A*) and simulated (*B*) maps represent equipotential lines in −40 μV gradations Those in the difference map (*C*) represent equidifference lines drawn in similar gradations The map pattern of the measured map is multipolar and that of the simulated map is bipolar The difference map shows a circumscribed negative area surrounded by a neutral area and pincer like bilateral positive areas The area of epicardial breakthrough became enlarged (heavily shaded area) on the epicardial surface

measured and simulated maps at each of the corresponding 85 unipolar lead points at the corresponding instant was obtained by subtracting the potential value in simulated map from that in measured map the equidifference lines were then delineated in 40 μV gradations (difference map)

Errors in the difference maps were mainly due to errors in the simulated maps in the determination of the magnitude and direction of the resultant electromotive force from the corrected orthogonal lead system These errors were estimated by the following way The magnitudes of lead vectors of the corrected orthogonal X Y and Z leads were modified by plus or minus twice their standard deviation and the error range of simulated potential calculated from these values was ±40 μV Thus a difference in potential value between the measured and simulated maps of less than ±40 μV was considered to be insignificant

Results

When the artificial perfusion of the canine hearts was continued for more than about 1½ hours most of the hearts became edematous and the QRS complex in the time reference ECG showed increased duration and decreased amplitude There were however three successful cases where the increase of QRS duration was less than 3 per cent and the decrease of QRS amplitude was less than 20 per cent of the control in the time reference ECG In one of them the process of the epicardial breakthrough was well represented even in the measured map probably owing to a

Fig 7 A difference map obtained at 13 5 msec after the onset of ventricular activation was superimposed on the figure of the heart showing the spread of epicardial breakthrough of ventricular activation (heart frontal view) Both were drawn in almost the same reduced scale Note that the central neutral area of the difference map is just facing the area of epicardial breakthrough

slight forward displacement in cardiac location compared to the other two cases Since the general feature of the change in the difference map was almost identical in these three cases the data on one case serve for the following description

The process of ventricular activation was shown by isochronic lines for each 5 msec interval as shown in Fig 2 The earliest arrival of the activation front at the epicardial side of the myocardium occurred 8 msec after the onset of ventricular activation at the anterior wall of the right ventricle Thereafter the activation front spread rapidly into the right and left ventricular walls showing a delay at the outflow tract and nearby region of the right ventricle before finally reaching the posterolateral base of the left ventricle The epicardial side of the pulmonary conus was affected about 44 msec after the onset of ventricular activation The activation process thus obtained resembled closely that reported by other researchers[4-14] except for the somewhat longer duration required for depolarization in the present experiment This might be due to the lower temperature of the experimental Tyrode's solution

At 3 msec after the onset of ventricular activation the activation front had not yet arrived at the epicardial side as seen in Fig 2 The map patterns of both measured (Fig 3 *A*) and simulated (Fig 3 *B*) maps closely resembled each other the potential maximum appearing slightly below the respective center of the map and the equipotential lines showing a rather smooth running, almost concentric configuration In the difference map (Fig 3, *C*), no striking difference in potential was observed Where as in this case the maximum difference in potential was insignificant (less than $\pm$ 40 μV), the area was called neutral and represented by a dotted zone

At 6 msec after the onset of ventricular activation, the activation front had not arrived at the epicardial side either (see Fig 2) Although the potential maximum was found in the same place in both measured and simulated maps (Fig 4 *A* and *B*), there was a significant difference in potential value In the difference map (Fig 4 *C*) a circumscribed area with a positive difference value appeared slightly to the right of the map center

By 13 5 msec after the onset of ventricular activation, epicardial breakthrough of the activation front had occurred, as shown by the shaded area of the heart seen on the left in Fig 5 In the measured map (Fig 5, *A*), the equipotential lines showed a complex bending toward the maximum located slightly to the right of the map center reflecting a decrease in their potential In the simulated map (Fig 5 *B*) the maximum was located somewhat similarly though a little nearer to the center The equipotential lines, however were smooth rather concentric in shape unlike those of the measured map The zero line of the measured map (Fig 5 *A*) descended gradually shifting leftward as it approached the bottom, in the simulated map (Fig 5, *B*) it shifted to the right in gradual fashion In the difference map (Fig 5, *C*) the broad positive area with a maximum on either side was seen extending downward from central part of the map A circumscribed neutral area was seen in the middle

At 22 5 msec the area of the epicardial breakthrough became more extensive In the measured map (Fig 6 *A*) there was a so called multipolar distribution a minimum of great negative potential emerged slightly to the right of the center of the map a maximum with great positive potential was seen just above and to the left of the center and a maximum and minimum with less peak values were noted at the very lower right In the simulated map (Fig 6 *B*) only one maximum and one minimum were recognized in areas corresponding to those of the great maximum and minimum in the measured map (Fig 6 *A*) The

potentials however were less than the corresponding maximum and minimum in measured map

In the difference map (Fig ■ C) there appeared a localized negative difference area at a part slightly below and to the right of the map center This newly appearing negative area was seen at 13.5 msec inside the circumscribed neutral area

Discussion

In electrocardiology it is well known that an electric double layer seemingly appears at the boundary of the activated and resting regions of the myocardium with positive charges on the resting side and it changes in extent and location following the propagation of ventricular activation

According to many data on experimental dogs recorded by numerous authors the ventricular activation initially occurring in the septal wall begins to spread into the nearby subendocardium In the anterior free wall the activation front spreads expansively along the endocardium and toward the epicardial side making the epicardial breakthrough first at a locus on the right anterior free wall The area of epicardial breakthrough also extends with the further spread of activation as shown in Fig 2 During the period up to the epicardial breakthrough the electric potential at each lead point facing the activation front keeps gaining positivity

Once the epicardial breakthrough occurs the electric double layer disappears from the area of epicardial breakthrough giving rise to a decrease in electric potential at lead points facing it This decrease in potential becomes more abrupt as the area of epicardial breakthrough expands since this area is usually very near those lead points on the anterior thoracic surface The sharp drop in potential at these lead points due to epicardial breakthrough ■ usually known either as the intrinsicoid deflection in precordial lead ECG or as the change in proximity potential Thus the measured map obtained from unipolar chest lead ECG s is considered to provide useful information on the localized events of ventricular activation since the precordial lead points are generally very near the epicardial surface The decrease in potential however becomes invisible or less evident at such lead points if the entire electric double layer is replaced by a single equivalent electric dipole placed at the ventricular center[2] [2] This is why the proximity potential may not be adequately expressed in a simulated map

The differences in potential at respective lead points caused by the real pattern of electric double layer and those caused by the equivalent single electric dipole hypothetically placed at the ventricular center are visualized in the difference map One of the most important reasons for the appearance of those differences is thought to be the proximity of the activation front with or without the area of breakthrough since the electromotive force caused by the change in the area of activation front should be essentially the same for measured and simulated maps except for its location against the lead points Therefore the difference map is also considered to give useful information on the spread of ventricular activation at any given instant

These preliminaries and other fundamentals make it possible to analyze the relationships between the spread of ventricular activation and the map patterns of measured and difference maps at each instant as follows

The difference map with the neutral area at 3 msec following the onset of ventricular activation (Fig 3 C) suggested that the activation front was still near the ventricular center at this stage Several experimental findings by other authors and the fact that the activation front had not yet arrived at the epicardial side seem to corroborate this

The increase in positive potentials in the measured map (Fig 4 A) and the appearance of a conspicuous localized positive value area in the difference map (Fig 4 C) at 6 msec may be ascribed to the extension of the activation front and more especially to its displacement toward the epicardial side of the anterior ventricular wall (proximity effect)

The mushrooming of the positive area and the increase of difference values in the difference map at 13.5 msec (Fig 5 C) would be the expression of the proximity potential caused by the activation front approaching the corresponding lead points The newly emergent neutral area in the central part of the positive area seems to reflect decreasing potential caused by the occurrence of epicardial breakthrough at an underlying region In fact epicardial breakthrough was observed at the anterior surface of the ventricle (Figs 2 and

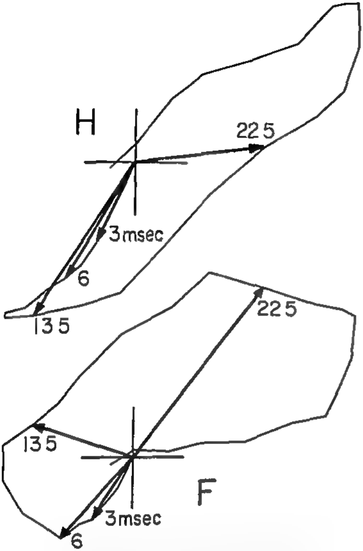

Fig 8 Horizontal (*H*) and frontal (*F*) loops of vectorcardiogram led from the cylinder surface through the corrected orthogonal lead system described in the text The arrows represent the instantaneous vectors at 3 6 13 5 and 22 5 msec respectively as shown by figures next to respective arrows

5) and the area of breakthrough was directly facing the circumscribed neutral area of the difference map as illustrated in Fig 7 The area of epicardial breakthrough was, supposedly, not wide enough, however to cause the negative potentials in the measured map against the positive potentials resulting from the underlying entire activation front

This finding was considered to lend strong support to the explanation of the analogous phenomenon observed in the human torso model experiment in the previous paper i e the appearance of the circumscribed negative area surrounded by a neutral area in the precordial part of the difference map was caused by epicardial breakthrough of the activation front

The appearance of a small but definitely positive area between the strongly negative area extending up toward the center and the less markedly negative area down near the right lower corner of the measured map at 22 5 msec (Fig 6 *A*) is a phenomenon analogous to the saddle distribution of Taccardi[1,2]

As may be seen in the map in Fig 6, the area of epicardial breakthrough became wider, the right side extending to the right lateral part Accordingly, the activation front was taken to be widely affecting the right and left ventricular free walls at this instant When the direction and magnitude of the instantaneous vector at this moment (Fig 8) were considered in the light of many other experimental findings[4,5,11,16] on the propagation process of ventricular activation it was supposed that the activation front had almost spread throughout the endocardial side of the left and right ventricular free walls except for the posterolateral part and conus pulmonaris area of the right ventricle and that most of the septal myocardium had already been fully depolarized by this time Therefore, the extensive negative area in the measured map (Fig 6 *A*) was supposed to be the expression of the great negative potential caused by the extensive area of epicardial breakthrough as analogously explained for the negative potential seen at a point directly facing an opening of closed surface electric double layer

The positive potential area at the upper left near the center of the map would mainly be the expression of potential caused by the positive side of the activation front as affecting the anterobasal part of the free wall near the anterior surface of the cylinder The narrow zone of positive potential would be caused by the activation front affecting the right lateral part of the right ventricular wall at this instant

The negative potential at lower right would be the one caused by the negative side of the wide activation front which was spreading toward the epicardial side of the left ventricle since it was possible to see this negative side receding from the corresponding part of the cylinder through the unactivated mural region between bilateral activation fronts at the posterolateral part of the right ventricle via the completely depolarized septal wall An analogous explanation was advanced by Taccardi[1,2] and later by Boineau and associates[4,5] who correlated the torso surface

potential distribution of experimental dogs with the ventricular activation process. Spach and associates[3] also came to a similar conclusion from the study of children undergoing cardiac surgery

The circumscribed negative area in the difference map which newly appeared in the central neutral area a part of which had been seen in the preceding stage (Fig 6 C) would have resulted from the increased negativity caused by the proximity of the extensive epicardial breakthrough area for reasons analogous to the ones stated before The positive area surrounding the neutral and negative areas was considered to be mainly the expression of proximity potential caused by the positive charges of the underlying activation front which was surrounding the area of epicardial breakthrough Therefore this difference map seems to express a pattern which is closely related with the spread of activation front at this instant Hereafter analogous relationships between map patterns and the spread of ventricular activation were also observed with other measured and difference maps obtained during the period of QRS duration but they gradually grew much simpler

This experiment confirmed the finding that the difference map reflects mainly the proximity potential at each instant of ventricular activation Therefore it was useful for the estimation of the spread of the ventricular activation when used in combination with the measured map especially in a period during which the activation front was affecting the anterior or anterolateral part of the ventricular free wall

Unlike the previous experiment on the human body the present one was performed under the condition that the electric conducting medium was homogeneous being the same both inside and outside of the heart Nevertheless serial difference map patterns similar to those in the previous paper emerged Therefore the interpretation of the difference map in the present paper would seem quite applicable to that in the human torso model experiment Serious divergences would not result simply because of the inhomogeneous electric conductance in the living human torso

Since the heart position in the cylinder was not simulated exactly as that in the canine thorax as described in the Methods section the pattern of the measured map might be somewhat atypical The exact simulation of the heart position in the cylinder was not central to this paper The essentials were to ascertain the sequence of ventricular activation and to pursue the mutual locational relationships between the ventricular surface and lead points

Summary

Three kinds of torso surface isopotential maps (measured simulated and difference maps) were delineated at every 1 5 (or 3) msec during the QRS duration from the 85 unipolar lead ECG s led from the surface of a cylindrical torso model filled with perfusate and containing a canine heart undergoing Langendorff's perfusion These three maps were compared as to the propagation process of ventricular activation obtained from the same heart and close correlations were found between the spread of ventricular activation and the map patterns of measured and difference maps

The difference map mainly reflected the proximity potential at each instant of ventricular activation in QRS duration and when used in combination with the measured map it was useful to estimate the spread of ventricular activation especially around the stage of epicardial breakthrough of the activation front

It was confirmed that the interpretation of the difference map expressed in the present paper would not be misleading even if applied to a difference map obtained in a human torso model experiment

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REFERENCES

1 Taccardi, B Distribution of heart potentials on the thoracic surface of normal human subjects, Circ Res. 12 341 1963
2 Taccardi, B Distribution of heart potentials on dog s thoracic surface Circ Res. 11 862 1962
3 Spach, M S Silberberg W P Boineau J P Barr R C Croft Long E Gallie T M Gabor J B and Wallace A G Body surface isopotential maps in normal children ages 4 to 14 years, Am Heart J 72 640 1966
4 Boineau, J P Spach M S Pilkington T C and Barr R C Relationship between body surface potential and ventricular excitation in the dog. Circ Res. 19 489 1966
5 Boineau, J P Hill, J D., Spach M S and Moore E N Basis of the electrocardiogram in right ventricular hypertrophy Relationship between ventricular depolarization and body surface potentials in dogs with spontaneous

RVH contrasted with normal dogs AM HEART J 76 605 1968
6 Horan L G Flowers N C and Brody D A Body surface potential distribution Comparison of naturally and artificially produced signals as analyzed by digital computer Circ Res 13 373 1963
7 Frank E Determination of the electrical center of ventricular depolarization in the human heart AM HEART J 49 670 1955
8 Toyoshima H, Wada M Sugiyama S Sugenoya J Toyama J and Yamada K Sequential change in the difference of potential distribution between a normal subject and simulated torso model Jap Heart J 15 560 1974
9 Scher A M Ohm W W Kerrick W G L Lewis S M and Young A C Effects of body surface boundary and of tissue inhomogeneity on the electrocardiogram of the dog Circ Res 29 600 1971
10 Brody D A A theoretical analysis of intracavitary blood mass influence on the heart lead relationship Circ Res 4 731 1956
11 Itatsu H Theoretical interpretation of contiguous bipolar ECG and its relationship to the time of arrival of activation Part 1 Some fundamental studies Jap Circ J 18 1 1954
12 Sodi Pallares D Barbato E and Delmar A Relationship between the intrinsic deflection and subepicardial activation AM HEART J 39 387 1950
13 Tatematsu H Wada M Okajima M and Yamada K On line conversational mode processing system for body surface mapping as designed for clinical application—An example WPW syndrome Adv Cardiol 10 20 1974
14 Nagaya T Studies on the spread of the ventricular activation in experimental right bundle branch block Jap Circ J 23 503 1957 (translated into English in Ref 20)
15 Scher A M and Young A C Ventricular depolarization and the genesis of QRS Ann N Y Acad Sci 65 768, 1957
16 Sodi Pallares D Rodriguez M I Chait I O and Zuckermann R The activation of the interventricular septum AM HEART J 41 569 1951
17 Wilson F N Macleod A G and Barker P S The distribution of the action currents produced by heart muscle and other excitable tissues immersed in extensive conducting media J Gen Physiol 16 423 1932 33
18 Woodbury L A Woodbury J W and Hecht H H Membrane resting and action potentials of single cardiac muscle fiber Circulation 1 264 1950
19 Toyoshima H Studies on electrocardiograms and vectorcardiograms by means of reconstruction methods, Jap Circ J 27 73 1963
20 Toyoshima H Reconstruction method of ECG and VCG and its application to clinical diagnosis Nagoya, Japan 1972 Nakanippon Printing Co Inc
21 Wilson F N Johnston F D Rosenbaum F F Erlanger H Kossman C H Hecht H Cotrim N de Oliveira R M Scarsi R and Barker P S The precordial electrocardiogram AM HEART J 27 19 1944
22 McFee R and Parungao A On the interpretation of cancellation experiments AM HEART J 58 582 1959
23 McFee R On the interpretation of cancellation experiments II AM HEART J 59 433 1960
24 Nelson C V Human thorax potentials Ann N Y Acad Sci 65 1014 1957
25 McFee R and Johnston F D Electrocardiographic leads I Introduction Circulation 8 554 1953
26 Horan L G Flowers N C and Brody D A Principal factor waveforms of the thoracic QRS complex Circ Res 15 131 1964
27 Okada R H A critical review of vector electrocardiography IEEE Trans Biomed Electronics 10 95 1963

Comparison of the coronary collateral circulation in dogs and baboons after coronary occlusion

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Although the dog has served as the experimental model in innumerable studies of coronary occlusion and myocardial infarction questions have frequently been raised about the applicability of findings of such studies to man The present study was therefore undertaken in order to compare the effects of coronary occlusion in the dog and a species phylogenetically much closer to man the baboon

Methods

Dog studies Nineteen healthy male mongrel dogs were anesthetized with sodium pentobarbital (25 to 30 mg per kilogram of body weight) intubated and placed in the right lateral decubitus position Respiration was assisted by means of a Harvard Respiration Pump to assure adequate ventilation Under fluoroscopy Goodale Lubin catheters were advanced by way of neck and femoral vessels to the aortic root coronary sinus the right atrium A modified single end hole No 8 Fr Sones catheter was advanced to either the left anterior descending (LAD 10 dogs) or left circumflex (LCA nine dogs) branch of the main left coronary artery

Statham pressure transducers (P23Db) were placed at mid thoracic level for measurement of pressures with right atrial pressure recorded at high sensitivity (1 mm Hg equal to 4 mm of paper) To prevent clotting catheters were flushed with heparinized saline solution throughout the study Pressures and electrocardiograms (ECG) were recorded on an Electronics for Medicine DR 8 recorder

Coronary blood flow (CBF) was determined in milliliters per 100 Gm by intracoronary injection of Kr in saline by means of precordial scintillation counting (*Picker Nuclear Omniprobe*) with an Esterline Angus recorder Blood samples were obtained from the aorta and coronary sinus for determination of pH and Po (Radiometer Electrodes) and to assure normal hematocrit Oxygen saturation was determined by using the oxyhemoglobin dissociation curve of the dog Coronary resistance (CR) was expressed in units calculated from the formula CR = (AO − RA) × 100/CBF where Ao is mean aortic pressure RA is right atrial pressure and CBF coronary blood flow in milliliters per 100 Gm of tissue

After control measurements were obtained the intracoronary Sones catheter was advanced and wedged into a distal branch of either the LAD or LCA as previously described (Fig 1) This results in an ischemic area averaging 13 per cent of LV weight Coronary collateral blood flow (CCBF) was thereafter measured over a 2 to 3 hour period by recording Kr washout curves obtained by injection through the end hole distal to the obstruction and coronary collateral resistance was calculated by inserting the CCBF in the resistance formula above No differences in these variables measured after either 2 or 3 hour occlusions have been found by us previously

In six dogs after 2 hours of ischemia had elapsed an intravenous infusion of isosorbide

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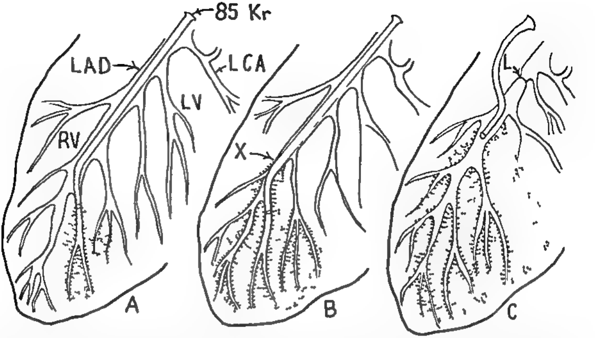

Fig 1 Experimental preparation demonstrating methods of coronary occlusion In examples *A* and *B* a catheter has been wedged into a distal branch of the LAD but in *B* where LAD is smaller than *A* (usually the case with baboons) the LAD is occluded more proximally (indicated by point X) and thus a larger area of ischemia (stippled) results Example *C* illustrates an open chest animal where the LAD has been ligated (*L*) and tubing inserted distally for isotope injection to an area of ischemia somewhat larger than in the other examples *LAD* left anterior descending branch *LCA* left circumflex branch *RV LV* right and left ventricles

dinitrate in saline was administered (12 5μg per kilogram of body weight per minute in approximately 1 ml volume per minute) The effects of this infusion on pressures and flows were evaluated after 30 minutes

In 13 dogs, before they were put to death an additional bolus of [85]Kr was infused into the involved myocardium through the wedged catheter and thoracotomy was rapidly performed while under direct vision a small amount of Evans Blue (3 to 5 ml) was infused to outline the central ischemic area In order to sample tissue at the optimal time to evaluate inner to outer wall isotope count ratios the hearts were arrested by iced Ringer's lactate solution and right ventricular compression 2 minutes following isotope injection This timing was chosen since the transmural gradient of isotope reflecting greater subendocardial ischemia is largest then Samples were obtained from the central ischemic area and a nonischemic portion of the LV, i e in the distribution of the other patent main left coronary branch The wall thickness was grossly divided into inner one third (subendocardium) and outer two third samples to determine counts per minute per gram and expressed as ratio of inner third/outer two thirds activity These samples were homogenized in distilled water and analyzed for potassium and sodium on an autoanalyzer with flame photometry attachment Total heart weight and that of the left ventricle including the septum were measured

Baboon studies Mature male baboons were premedicated with intramuscular phencyclidine (Sernylan) (1 mg per kilogram of body weight) and then intravenous sodium pentobarbital was administered for general anesthesia (usually 15 to 20 mg per kilogram of body weight)

Initially attempts were made in all baboons to accomplish catheter wedge occlusion but this was accomplished in only four In two additional animals the chest was opened and the LAD ligated 1 0 to 1 5 cm beyond its origin with a small polyethylene catheter (PE60) inserted distally for the injection of [85]Kr in saline Control preocclusion coronary blood flows in these two animals were determined by retrograde injection of isotope through a catheter placed high in the coronary sinus [1] In preliminary studies of seven baboons no significant effect of thoracotomy on Ao pressure CBF coronary resistance or heart rate was found Therefore the data from these two ligation animals were pooled with those of the four baboons with wedge occlusions for statistical comparisons of hemodynamics with the dogs

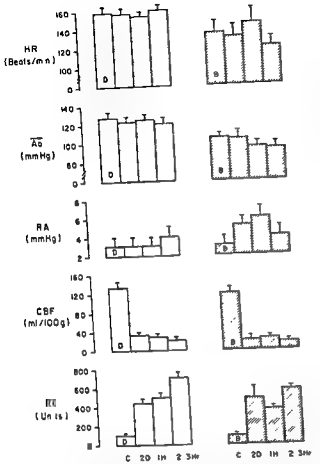

Fig 2 Coronary hemodynamics in 13 dogs (*D* clear bars) and six baboons (*B* shaded bars) showing mean values and standard errors of mean pre and postcoronary occlusion up to 3 hours without nitrate administration Within each group heart rate and aortic pressure did not change significantly throughout the observation period RA pressure rose significantly only in baboons at 1 hour CBF fell to approximately 25 per cent of control after occlusion remaining at this level throughout the observation period Rc calculated during the postocclusion period ranged from four to seven fold that of the control status in both groups *HR* heart rate *Ao* mean aortic pressure *RA* right atrial pressure *CBF* coronary blood flow for control (C) and coronary collateral blood flow thereafter *Rc* coronary resistance and coronary collateral resistance before and after occlusion respectively Times indicated are those elapsed following wedge or ligation occlusion

In four other baboons ligation of the LAD was performed but data obtained were limited to Ao and high CS blood gas studies pressures plus tissue sampling in two A total of 16 baboon hearts from these and other adult animals were examined for gross anatomical features to compare with dogs

In the dogs no antiarrhythmic agents were administered after wedging in order to preclude

Table I Cardiac weight dogs vs baboons (mean ± S E M)

	Body weight (kg)	*Heart wt / body wt (Gm /kg)*	*LV* wt /total heart wt*
Dogs (n = 18)	22.3 ± 0 8	7.9 ± 0 2	0 67 ± 0 03
Range	18 1 32 0		
Baboons (n = 16)	?0 0 ± 1 4	5 2 ± 0 3	0 64 ± 0 01
Range	13.0-?4 6		
P value	NS†	< 0 001	NS

LV = free l ft tricular wall plus septum
†NS = not significant (P ≥ 0 1)

Table II Control coronary hemodynamics and metabolism (mean ± S E M)

	Dogs (n = 19)	*Baboons (n = 6)*	*P values*
HR (b p m.)	1?8 ± 6	13? ± 11	< 0 1
Ao (mm Hg)	127 ± 6	103 ± 4	< 0 01
RA (mm. Hg)	3 ± 1	3 ± 1	NS
CBF (mL/100 Gm.)	136 ± 11	121 ± 9	NS
Rc (units)	96 ± 6	86 ± 7	NS
pH	7 41 ± 0 0?	7 4? ± 0 01	< 0 01
Sa_{O_2} (%)	9? ± 1	97 ± 1	< 0 1
Pa_{O_2} (mm Hg)	91 ± 5	93 ± 5	NS
Pcs_{O_2} (mm Hg)	34 ± 4	3? ± 3	NS
$Pa\text{-}cs_{O_2}$ (mm Hg)	57 ± 3	61 ± 6	NS

HR = He rt rate Ao = aort c pressure RA = right atrial p essu e CBF = co nary blood flow Rc = coronary resistan e Sa_O = arterial oxygen saturation P_O = partial pressure f oxyg n in arterial blood Pcs_O = partial pressure of o ygen in coro ary inus blood.

Table III Inner wall/outer wall distribution of Kr after occlusion

Dogs		Baboons
A No drug	*B Nitrate*	*C Nitrate*
0 80	0 ?3	0 81
0 0	0 4	0 2?
0 33	0.?6	0 ?7
0 9?	1.30	0 ?6
0 92	0.84	0 39
0 5	1 07	
0 8		
0 ?†	0.83†	0 52†
±0 08	±0 13	±0 09

Four wedge plus one l gat baboon.
†d ± S E M

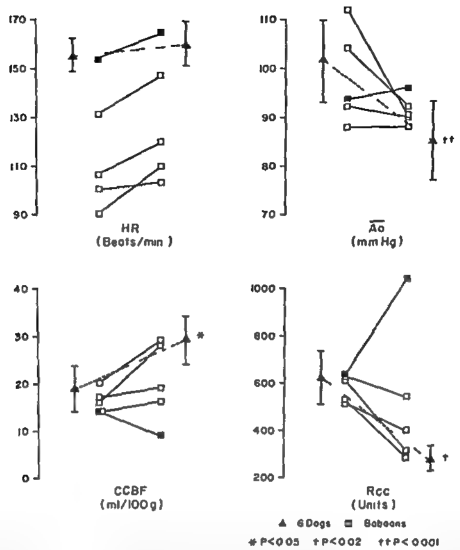

Fig 3 Effects of 30 minutes intravenous infusion of isosorbide dinitrate in six dogs (mean value and S E M indicated by solid triangles) and five individual baboons (squares) after 2 hours of coronary occlusion With one exception (solid square) the baboons responded similarly to dogs with tendency toward increase of heart rate fall in aortic pressure increased coronary collateral blood flow (*CCBF*) and a decrease in coronary collateral resistance (*Rcc*)

any possible effects of such treatment on the data obtained This results in about a 10 to 15 per cent loss from ventricular fibrillation following wedge occlusion Preliminary studies in baboons however resulted in ventricular fibrillation almost universally after either catheter wedging or ligation Of the four successful baboon wedge studies one required no treatment ventricular fibrillation occurred in the other three requiring external DC shock for reversion to normal sinus rhythm All the ligation baboons with one exception required one to four DC shocks (10 to 15 joules to the heart) to reverse ventricular fibrillation Procaine amide (200 to 800 mg total) was also administered in divided doses no hemodynamic data were obtained for at least 15 minutes following drug administration when prior blood pressure appeared restored

Pressures and flows were recorded in the baboons (with the above modifications) as in the dogs with isosorbide dinitrate infusions in five after 2 hours of ischemia and similar studies for anatomy and ischemia post mortem

Student s t test was used for statistical analysis of the data The grouped t test was used for comparison of dogs and baboons the paired t test for changes within each group of animals

Results

Although there were no significant differences in body weight between the dogs and baboons studied (Table I) nor difference in LV/total heart weight ratios the ratio of heart weight to total body weight was less in the baboons than in the dogs and similar to that found in man (mean 5 2 Gm per kilogram in baboons and 5 3 Gm per kilogram in man[7])

Hemodynamics Control coronary hemody

Table IV Tissue electrolytes (mean ± S E M)

	Potassium (μEq/Gm)				Sodium (μEq/Gm)			
	Ischemic		Nonischemic		Ischemic		Nonischemic	
	Inner	Outer	Inner	Outer	Inner	Outer	Inner	Outer
Dogs								
No iso† (n = 7)	45 ± 2	48 ± 3	6[illegible] ± 4	69 ± 2	60 ± 3	56 ± 3	44 ± 1	42 ± 1
Iso (n = 6)	4[illegible] ± [illegible]	46 ± 3	[illegible]0 ± 2	74 ± [illegible]	61 ± 4	60 ± 4	39 ± 2	37 ± 1
Baboons								
No iso (n = 3)	37 ± 3	41 ± 4	69 ± 3	[illegible]6 ± 3	63 ± 5	[illegible]4 ± 2	53 ± 7	53 ± 7
Iso (n = 5)	39 ± 5	49 ± 4	[illegible]5 ± 5	77 ± 4	[illegible]5 ± 5	[illegible]5 ± 4	53 ± 2	[illegible]2 ± 4

Inner = inner one third wall thickness Outer = outer two third wall thickness

†Iso = isosorbide dinitrate treated

namics and metabolic status in dogs and baboons are compared in Table II Higher systemic pressures were found in the dogs Efforts to achieve arterial Po_2 values similar to those obtained in dogs resulted in slight hyperventilation of the baboons (average pH 7 47)

The effects of coronary occlusion without nitrate in the two groups are compared in Fig 2 Within each group followed 2 to 3 hours after occlusion the patterns of response were quite similar Heart rate and aortic pressure did not change significantly Among the baboons only at 1 hour after occlusion the right atrial pressure rose significantly (from 3 to 6 mm Hg) when compared with control ($p < 0.05$) Following coronary occlusion CCBF was approximately 25 per cent of control CBF in both groups with coronary resistance increasing four to sevenfold throughout the observation period

Arterial oxygen tension saturation and pH did not change significantly throughout the study in either the dogs or the baboons Despite high coronary sinus sampling with LAD occlusion neither in these animals nor in those with LCA occlusion were increased coronary arteriovenous Po differences found reflecting the small ischemic area size in relation to the normal ventricular mass sampled in the coronary sinus effluent Only in the dogs with LAD occlusions of 2 to 3 hours duration was a significant coronary sinus Po reduction found (mean 34 ± 4 [S E M] mm Hg in control falling to mean of 29 ± 3)

The effect of isosorbide dinitrate on the ischemic coronary circulation is illustrated in Fig 3 where the individual effects in five baboons are compared with the mean results in six dogs With one exception the same response pattern was observed a tendency toward increase in heart rate reduced arterial pressure increased CCBF and decreased coronary collateral resistance

Transmural isotope distribution In Table III the transmural distribution of Kr injected distal to an occlusion just prior to killing is indicated in three groups of animals untreated dogs dogs administered the drug following occlusion and baboons similarly treated Ratios of less than one in all three groups signify a greater flow reduction to the inner third of the wall as compared to the outer two thirds There was no effect of isosorbide dinitrate on this ratio in the dogs Although the treated baboons in general had ratios somewhat less than the treated dogs the differences was not significant at the 5 per cent level

Tissue electrolytes Changes after ischemia in myocardial K and Na were similar in dogs and baboons and unaffected by nitrate administration (Table IV) K was lower and Na higher in the ischemic areas when compared to nonischemic areas with these differences highly significant statistically ($P < 0.01$ or < 0.001 three untreated baboons not analyzed statistically)

Although there was a trend toward lower K in the inner wall when compared with the outer wall in both ischemic and nonischemic areas these differences were not statistically significant

Discussion

The controversy over the presence or absence of coronary collaterals in the normal human heart has been a long one and cogently summarized by Fulton whose detailed studies have demonstrated that in the human subject they are present but primarily subendocardial and intramural Thus the presence and extent of these

vessels has been more difficult to demonstrate and appreciate than the more obvious subepicardial collaterals supplying the inner wall in the dog. With the proof of such vessels demonstrated in the normal human heart,[8] it was the object of the present study to determine whether or not the coronary collateral circulation in a primate would respond in a manner similar to that of the dog following coronary occlusion.

Technical considerations. As originally designed, this study was to treat the dogs and baboons in an identical manner experimentally. We soon learned that this was not practicable. Unlike the relatively passive canine, the adult male baboons required sedation before they could be approached for the administration of intravenous barbiturates. Anatomic factors also altered our approach. As others have previously reported,[9] we found the baboon heart to be smaller in relation to body size than the dog. Furthermore, the dog has a very small right coronary artery and thus invariably sizable left main coronary branches, whereas the baboon has a substantial right coronary artery sharing in the distribution of coronary flow. Both of these factors no doubt account for our finding smaller LAD and LCA branches in baboons on gross examination when compared to dogs of similar body weight. This made them more difficult to cannulate under fluoroscopy and, even when this was possible, wedging usually occurred at a higher level than in the dogs, as noted when thoracotomy was performed prior to killing (see Fig. 1). This factor no doubt contributed to the high rate of fatal ventricular arrhythmias that occurred in the baboons without treatment. After losing a number of baboons in this way we elected to utilize DC countershock and procainamide in order to salvage an adequate number of animals for study. Finally, even prior to occlusion the baboons were slightly hyperventilated to maintain arterial oxygen levels similar to those in the dogs and had lower aortic pressure when compared to the latter.

Consideration must be given to the possible influence of these factors in the baboons before their data can be compared with those of the dogs.

Phencyclidine has been widely used in simian primates with a high degree of safety and no marked cardiovascular effects noted.[10,1] As used in the present study it is probable that even the sedative effect initially desired had ended by the time of coronary occlusion. Procainamide has been reported to have adverse hemodynamic effects in chronically diseased human hearts,[14] but more recent detailed animal studies[1,17] have revealed no negative inotropic effects of the drug. DC countershock has also been hemodynamically well tolerated in thoracotomized dogs.[1]

Myocardial potassium loss has been shown to occur in dogs during both ischemia[1] and external A C countershock,[1] with procainamide effecting at least transient reversal.[1] DC countershock directly applied to the dog heart at levels of 30 to 50 joules has caused burns.[1] Therefore, when required in thoracotomized baboons, DC shock was administered below these levels with small paddles (5 cm diameter) to areas of the heart that would not be later sampled for analysis. These interventions may have altered tissue cation levels in either direction. It is noteworthy, however, that in the one wedge baboon requiring neither DC shock nor procainamide the same pattern of K loss was found as in the other animals (K in ischemic inner wall 25 μEq per gram, as opposed to 62 μEq per gram in nonischemic inner wall).

Marked respiratory alkalosis with hyperventilation in anesthetized dogs (pH raised from 7.36 to 7.62) has been shown to have no significant effect on coronary flow, cardiac output or systemic pressure. The slight increase in arterial pH among the baboons when compared to the dogs might therefore not be expected to have had a major effect on results obtained. Within each group the pH remained constant throughout the study.

Thus, although the differences in the handling of the two groups were unavoidable, we believe that the results obtained might reasonably be compared in a qualitative if not strictly quantitative manner.

Significance. The canine data obtained in this study regarding coronary collateral blood flow (CCBF) are in accord with those obtained by isotopic washout methods in this and other laboratories in the past,[1] with CCBF ranging from 20 to 30 per cent of control flow in anesthetized dogs immediately following occlusion and persisting up to 6 hours of observation. Coronary flow data in primates, on the other hand, have been limited and only in one instance, to our knowledge, have been directly compared to those

from a concurrently studied group of dogs Grayson and Irvine [3] using a heat clearance method to evaluate myocardial blood flow in contrast to the dog studies mentioned above found a 50 per cent immediate reduction in flow after coronary occlusion with a fall to zero levels after about 5 hours in both dogs and monkeys A possible reason for this discrepancy was proposed in a later study in which they measured both heat clearance and production The latter paralleled the postocclusion changes reported by the isotopic clearance methods and it was postulated that heat production and isotope clearance were more related to the nutritional flow of the active capillary circulation whereas the heat clearance reflected nonnutritional flow

A more recent study by Lubbe and associates of coronary occlusion in open chest baboons evaluated distribution of myocardial blood flow with radioactively labeled microspheres Forty minutes following ligation calculated flows were approximately 25 per cent of that in the normal myocardium but no conclusions could be drawn regarding transmural flow distribution because of the small numbers involved

Using krypton 85 we found similar patterns of CCBF in dog and baboon In both groups a greater flow reduction to the subendocardial wall in ischemia was demonstrated by transmural isotope distribution in agreement with previous reports by this and various other methods Similarly lower myocardial K and higher Na were found in the ischemic area as previously reported In contrast to a previous study from our own laboratory however a transmural ionic gradient was not found but differences in timing of tissue sampling and therapeutic interventions may account for these differences

The coronary collateral response to nitrate administration is of particular interest in view of the recent introduction of vasodilator therapy in acute myocardial infarction Hemodynamically both species respond similarly in a manner previously reported in dogs with an increase in CCBF and decrease in calculated resistance Unlike previous studies with partial occlusion or shorter occlusions lasting about 30 to 40 minutes the inner/outer wall distribution of isotope was not affected by nitrates in the present study This suggests that more prolonged ischemia may render the inner wall less responsive to flow distribution effects seen with nitrate administration at earlier stages Whether or not the salutary effects of nitrate on over all myocardial oxygen requirements may affect the periphery of the ischemic area differently and result in reduction of ultimate infarct size requires further quantitative study

Summary

The relevance to man of experimental observations on coronary collateral blood flow (CCBF) in dogs has been questioned The effect of 2 to 3 hour coronary occlusions in the anesthetized dog and a primate the baboon were therefore compared with CCBF measured by injections of Kr distal to occlusion with precordial counting Before killing additional isotope was infused to compare inner/outer wall flow distribution and myocardial tissue samples were analyzed for electrolyte content Effects of nitrates on hemodynamics and metabolism were also compared in dog and baboon Similar values for CCBF and resistance following occlusions were found in dog and baboon (flow approximately 25 per cent control calculated resistance increase four to sevenfold) Greater subendocardial ischemia in both species was indicated by isotope distribution less to the inner wall but electrolyte changes (K less and Na greater in the ischemic area compared to nonischemic) were similar transmurally in both species Hemodynamic responses to nitrate infusion (isosorbide dinitrate) were similar with increase in CCBF and decrease in resistance In neither group were inner/outer wall isotope distribution or electrolyte changes influenced by nitrate The coronary collateral response to occlusion is similar in dog and baboon in terms of both hemodynamics and metabolic changes After 2 to 3 hours of coronary occlusion some hemodynamic benefit may be demonstrated with nitrates but no metabolic advantage at least in the central area of ischemia

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REFERENCES

1 Kleinman L I and Radford E P Jr Ventilation standards for small animals, J Appl Physiol 19 360 1964

2 Herd J A Hollenberg M Thorburn G D Kopald H H and Barger A C Myocardial blood flow determined with krypton 85 in unanesthetized dogs, Am J Physiol 203 122 1962

3 Severinghaus J W Blood gas calculator J Appl Physiol 21 1108 1966
4 Weisse A B Senft A Khan M I and Regan T J The effect of nitrate infusions on the systemic and coronary circulations following acute experimental myocardial infarction in the intact dog Am J Cardiol 30 362 1972
5 Regan T J Oldewurtel H A and Ettinger P O Regional coronary blood flow during ischemia or epinephrine Relation to myocardial potassium and triglyceride In Maseri A editor Myocardial Blood Flow in Man Torino 1972 Minerva p 425
6 Harman M H Markov A Lehan P H Oldewurtel H A and Regan T J Coronary blood flow measurements in the presence of arterial obstruction Circ Res 19 632 1966
7 Grande F and Taylor H L Adaptive changes in the heart vessels and patterns of control under chronically high loads In Hamilton W F and Dow P editors Handbook of physiology Sec II Circulation Vol III Washington D C 1965 American Physiological Society p 2615
8 Fulton F M The coronary arteries Springfield Ill 1965 Charles C Thomas Publisher
9 Hermann G R Vice T E McGill H C Strong J and Werthessen N T The heart of the wild Kenya African baboon Normal control series of heart weight to body weight ratios In Vagtborg H editor The baboon in medical research Texas Press 1965 University of Austin p 265
10 Chen G Ensor C R Russel D and Bohner B The pharmacology of 1 (1 phenylcyclohexyl) piperidine HCl J Pharmacol Exp Ther 125 127 241 1959
11 Melby E C and Baker H J Phencyclidine for analgesia and anesthesia in simian primates J Am Vet Med Assoc 147 1068 1965
12 Vondruska J Phencyclidine anesthesia in baboons J Am Vet Med Assoc 147 1073 1965
13 McClendon R L Hansen W R and Kinsmon J M Hemodynamic changes following procainamide administered intravenously Am J Med Sci 222 375 1951
14 Harrison D C Sprouse J H and Morrow A G The antiarrhythmic properties of lidocaine and procainamide Circulation 28 486 1963
15 Austen W G and Moran J M Cardiac and peripheral vascular effects of lidocaine and procainamide Am J Cardiol 16 701 1965
16 O Rourke R A Bishop V S Stone H L and Rapaport E Lack of effect of procainamide on ventricular function in conscious dogs Am J Cardiol 23 238 1969
17 Hammermeister K E Boerth R C and Warbasse J R The comparative inotropic effects of six clinically used antiarrhythmic agents Am Heart J 84 643 1972
18 Yarbrough R Ussery G and Whitley J A comparison of the effects of A C and D C countershock on ventricular function in thoracotomized dogs Am J Cardiol 14 504 1964
19 Regan T J Harman M A Lehan P H Burke W M and Oldewurtel H A Ventricular arrhythmias and K transfer during myocardial ischemia and intervention with procainamide insulin or glucose solution J Clin Invest 46 1657 1967
20 Regan T J Markov A Oldewurtel H A and Harman M A Myocardial K loss after countershock and the relation to ventricular arrhythmias after nontoxic doses of acetyl strophanthidin Am Heart J 77 367 1969
21 Rivkin I M The defibrillator and cardiac burns J Thorac Cardiovasc Surg 46 755 1963
22 Rowe G G Castillo C A and Crumpton C W Effects of hyperventilation on systemic and coronary hemodynamics Am Heart J 63 67 1962
23 Redding V J and Rees J R Early changes in collateral flow following coronary artery ligation The role of the sympathetic nervous system Cardiovasc Res 2 219 1968
24 Haft J I and Damato A N Measurement of collateral blood flow after myocardial infarction in the closed chest dog Am Heart J 77 641 1969
25 Grayson J and Irvine M Myocardial infarction in the monkey Studies on the collateral circulation after acute coronary occlusion Cardiovasc Res 2 170 1968
26 Grayson J Robertson M and Scott C Heat clearance and heat production studies in acute experimental coronary occlusion Cardiovasc Res 7 220 1973
27 Lubbe W F Leisach M Lretorius [illegible] Bruyneel K J J and Opie L H Distribution of myocardial blood flow before and after coronary artery ligation in the baboon Relation to early ventricular fibrillation Cardiovasc Res 8 478 1974
28 Becker L C Fortuin N J and Pitt B Effect of ischemia and anginal drugs on the distribution of radioactive microspheres in the canine left ventricle Circ Res 28 263 1971
29 Griggs D M Jr and Nakamura Y Effect of coronary constriction on myocardial distribution of iodoantipyrine I Am J Physiol 215 1082 1968
30 Jennings R B Sommers H M Kaltenbach J P and West J J Electrolyte alterations in acute myocardial ischemic injury Circ Res 14 260 1964
31 Mathes P and Rival J Effect of nitroglycerin on total and regional blood flow in the normal and ischemic canine myocardium Cardiovasc Res 5 54 1971

Myocardial oxygen availability and cardiac failure in hemorrhagic shock

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Wiggers and Werle[1] were probably the first to suggest that a reduction in coronary blood flow may be responsible for irreversibility of the hemorrhagic shock syndrome The importance of low perfusion pressure and insufficient coronary flow leading to cardiac deterioration in shock animals has subsequently been emphasized by Sarnoff and associates and others The appearance of cardiotoxic factors and depression of the sympathoadrenal system have also been implicated as contributory to ultimate deterioration of cardiac function in shock But the relative contribution of myocardial failure to the severity and irreversibility of this process has been questioned

Earlier studies in our laboratory demonstrated a progressive reduction of myocardial contractility in shock which was attributed to the interplay of three key factors These included metabolic acidosis reduced coronary perfusion pressure and loss of sympathetic support More recent work has suggested from indirect evidence that myocardial oxygen availability may be closely related to the extent of myocardial depression

The present study was undertaken to ascertain by more direct methods the interrelationships between left ventricular function and myocardial oxygen availability and metabolism in sustained hemorrhagic hypotension A second objective was to determine whether the progressive and ultimately irreversible myocardial failure is related to impairment of myocardial metabolism and if this can be ascribed to inadequate coronary flow and oxygen delivery *to the myocardium*

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Methods

The studies were carried out on 18 adult mongrel cats of both sexes varying in weight from 2 2 to 4 5 kilograms and an additional 54 cats were used for donor blood A right heart bypass preparation was used (Fig 1) All animals were anesthetized by intraperitoneal sodium pentobarbital (30 mg per kilogram) The trachea was exposed and intubated The chest was opened in the midline and ventilation was maintained with a Harvard constant volume positive pressure pump Heparin (1 000 units) was given intravenously

The descending thoracic aorta was cannulated (Fig 1) and aortic flow was measured with a Statham 6 0 mm O D extracorporeal flow transducer and a Medicon K 2000 electromagnetic flow meter The aortic flow was then passed through a Sarns heat exchanger and returned to the descending aorta The azygous vein was ligated and the superior and inferior vena cavae were cannulated Systemic venous return including coronary was diverted to a venous reservoir (Fig 1) and then pumped through a specially constructed glass heat exchanger (Macalaster Bicknell Co) and back into the main pulmonary artery Coronary venous drainage was accomplished by passing a catheter into the right ventricular chamber through a stab wound in the wall and secured with a purse string stitch A T connector was placed in the line to permit temporary diversion of flow into a graduated cylinder for timed collections and for sampling

The extracorporeal tubing heat exchanger and

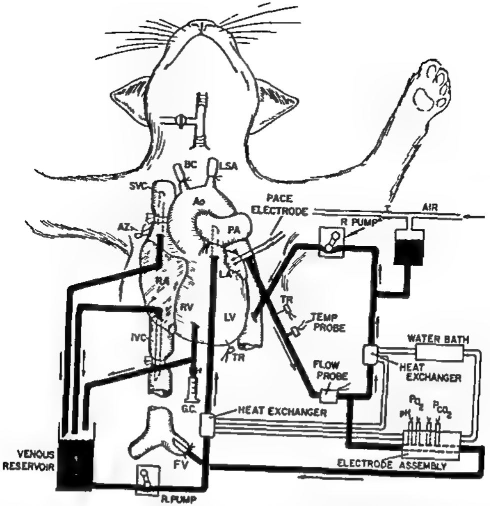

Fig 1 Diagram of right heart bypass preparation *TR* = pressure transducer *R pump* = roller pump *IVC* = inferior vena cava *LSA* = left subclavian artery *RA* = right atrium *RV* = right ventricle *AO* = aorta *FV* = femoral vein *GC* = graduate cylinder *SVC* = superior vena cava *BC* = brachiocephalic artery *AZ* = azygous vein *LA* = left atrium *LV* = left ventricle *PA* = pulmonary artery See text for detailed description

reservoirs were primed with freshly drawn heparinized (5 mg per kilogram) blood from donor cats Cephalic blood flow was abolished by ligating the brachiocephalic and left subclavian arteries Pulmonary and systemic flows were controlled independently by two roller pumps Aortic pressure was controlled with an adjustable constant pressure reservoir All pressure measurements were made with Sanborn transducers (267 series) The midlevel of the heart was used as zero reference Left ventricular pressure was measured by passing a 15 gauge needle through the apex into the left ventricular cavity The maximal rate of rise of left ventricular pressure (dP/dt max) was obtained with a R C differentiating circuit (time constant 0 268 msec) The heart rate was controlled by electrically pacing the left atrium with a Grass SD 5 stimulator Pressures, aortic flow, heart rate and left ventricular dP/dt measurements were recorded simultaneously on a multichannel oscillograph (Sanborn model 358) at a chart speed of 0 5 or 100 mm per second

Blood temperature was maintained at 38° ± 1° C and measured with a Yellow Springs probe and telethermometer Arterial pH P_{O_2} and P_{CO_2} were continuously monitored with a flow through electrode assembly with three Beckman 160 physiological gas analyzers and were frequently checked with a blood gas analyzer and pH system (Instrumentation Laboratories) Arterial and coronary venous blood samples were withdrawn simultaneously from the aortic and right ventricular cannulas for determination of oxygen content[15] and for measurement of pH P_{O_2} P_{CO_2} and hematocrit The hematocrit ratio was determined in duplicate by the method of microhematocrit tubes (Clay Adams) Myocardial oxygen consumption ($M\dot{V}_{O_2}$) and per cent oxygen extraction

Table I Hemodynamics values and oxygen metabolism in normotensive cats (N = 4)*

						Oxygen			Arterial			
Time (min)	AP	LVEDP	LV dP/dt max	CF	Myoc O avail	Art conc	C ext	MVO	pH	Po	Pco	Hct
0	15[illegible] ± 5 0	4 1 ± 0 3	2,210 ± 126	33 4 ± 1 7	22 19 ± [illegible] 6	7 77 ± 0 40	57 89 ± 3 61	13 3 ± 0 80	7 40 ± 0 03	106 8 ± 14 1	24 0 ± 2 2	16 9 ± 0 4
30	5 0 ± 5 0	3.9 ± 0 4	2,310 ± 63	41 9 ± 4 8	26 73 ± 3 [illegible]8	7 [illegible]9 ± 0 64	54 69 ± 2 03	15 54 ± 0.80	7 41 ± 0 01	104 8 ± 10 0	2[illegible] 8 ± 2.9	16 3 ± 1 3
60	5 0 ± 5 0	4 1 ± 0 4	2 332 ± 41	42 1 ± 8 8	30 30 ± 5 06	8 93 ± 0 75	51 39 ± 6 65	14.28 ± 1 14	7 42 ± 0 02	89.8 ± 11.8	24 4 ± 4 7	17 3 ± 1 5
90	[illegible]5 0 ± 5 0	5.5 ± 1 0	[illegible] 090 ± 84	37 6 ± 6 4	28 46 ± 5 17	8 68 ± 0 31	46 29 ± 10 42	11 38 ± 2 08	7 38 ± 0 03	98 3 ± 11 4	24 6 ± 3 1	18 1 ± 2.3

Values are mean ± standard error of the mean AP = mean arterial pressure in mm Hg. LVEDP = left ventricular end diastolic pressure in cm H_2O LV dP/dt max = maximal rate of rise of left ventricular pressure in mm Hg/sec CF = Coronary blood flow in mL/min Myoc O_2 avail = myocardial oxygen availability in ml./min /100 Gm heart weight Art conc = arterial oxygen content in vol% C ext = myocardial coefficient of extraction (A V)/(A) × 100 % MVo = myocardial oxygen consumption in ml./min /100 Gm heart weight pH in units. Po and Pco in mm Hg. Hct = hematocrit in %

Table II Hemodynamic values and myocardial oxygen metabolism in hypotensive cats

						Oxygen			Arterial	
	No	Time	LVEDP	LV dP/dt max	CF	Myoc O avail	C ext	MVO	pH	Hct.
Shock with LV failure (AP = 30 ± 5 mm Hg)	3	0	6 0 ± 0.9	1,[illegible]38 ± 131	17 2 ± 0 6	12 14 ± 1 66	73 42 ± 3.36	9 54 ± 0 50	7 36 ± 0 07	15 0 ± 1.2
		28 3 ± 3 0	32 3 ± 3 0	409 ± 88	11.5 ± 0.9	8 18 ± 0 87	65 [illegible]3 ± 2 59	5 29 ± 0.27	7.25 ± 0 07	15 3 ± 1.5
	6	0	5.5 ± 1 0	1 203 ± 145	15 9 ± 1 6	12 94 ± 1 [illegible]6	[illegible]6 12 ± 3.33	9 67 ± 0 71	7.37 ± 0 03	18.5 ± 1 7
		30	9 0 ± 0 9	[illegible] 4 ± 86	13 4 ± 1 5	11.82 ± 1 21	73 04 ± 2 05	7.99 ± 0 70	7.26 ± 0 05	18 7 ± 1 4
		55 2 ± 2 8	27 5 ± 3 9	535 ± 111	11.5 ± 1 2	9 44 ± 1 10	[illegible]6 15 ± 4 90	6.28 ± 0 71	7.25 ± 0 07	19 8 ± 1 7
Shock without LV failure (AP = 30 ± 5 mm Hg)	2	0	2.8 ± 0 2	1 [illegible] ± 2 5	13 [illegible] ± 0 4	13 37 ± 1 27	[illegible]0 06 ± 0 13	9.36 ± 0 86	7.36 ± 0 07	23 0 ± 0 0
		30	3 0 ± 0	1 581 ± 3 222	12 5 ± 1 1	13 05 ± 1 00	67 05 ± 0 67	8 [illegible]7 ± 1 11	7 23 ± 0 05	23.5 ± 0 4
		60	2 8 ± 0 2	1 570 ± [illegible]60	11 8 ± 0.2	13 20 ± 0 46	74 31 ± 3 99	9 91 ± 0.87	7 14 ± 0 06	23.5 ± 1 1
		90	3 0 ± 0 7	1 432 ± 3[illegible]8	11 5 ± 0 4	12 6[illegible] ± 0.56	[illegible]3 [illegible]0 ± 7 35	9 36 ± 1 35	7 09 ± 0 05	24 5 ± 0 4

Values are mean ± standard error of mean Abbreviations same as in Table I Asterisks (*) indicate statistically significant difference between time periods in each group p < 0.05 p < 0.01

were calculated Myocardial oxygen availability was estimated as the product of arterial oxygen concentration and coronary blood flow

In order to more readily demonstrate the effects of limitation of myocardial oxygen availability on ventricular performance in shock the oxygen carrying capacity was reduced by diluting the donor blood with an equal volume of 5 per cent glucose in saline The final hematocrit of the preparation was in the range of 15 to 25 per cent

(normal hematocrit for the cat is approximately 30 per cent)

After completion of all surgical procedures a period of 15 minutes was allowed for stabilization and control measurements were obtained with a mean aortic pressure of 75 ± 5 mm Hg Shock was induced by rapid bleeding from the aorta into the constant pressure reservoir and aortic pressure was set at 30 ± 5 mm Hg Samples were obtained every 30 minutes following the onset of hypotension (zero time) for a period of 90 minutes or until severe cardiac failure terminated the experiment

Four animals were studied in a manner similar to those described above except that mean aortic pressure was maintained at 75 ± 5 mm Hg throughout the experimental period These animals served as controls All data in this study were processed and analyzed by standard statistical methods[1] The difference was considered significant when the p value was less than 5 per cent

Results

Left ventricular performance and myocardial oxygen metabolism in normotensive animals The total right heart bypass preparation involves extensive surgical and cannulation procedures The relative stability and other characteristics of the preparation were therefore determined by studying four animals in which mean aortic pressure was maintained at 75 mm Hg for the full duration of the 90 minute study period The results are presented in Table I It is evident that there were no significant changes in left heart performance which might suggest failure Coronary flow increased modestly during the first 30 minutes and then showed little change Myocardial oxygen extraction and consumption showed small but statistically insignificant changes with time Arterial blood gases pH and hematocrit values also remained stable over the 1½ hour interval

Left ventricular performance and myocardial oxygen metabolism during hemorrhagic shock In 13 animals hemorrhagic shock was produced by lowering the mean aortic pressure to 30 mm Hg Of these two died with ventricular fibrillation shortly after the onset of hypotension Table II summarizes the hemodynamic and metabolic data obtained in the remaining 11 preparations Nine developed LV failure and two showed no evidence of failure during the 1½ hour shock period

Within 30 minutes of the onset of shock three animals showed a sharp reduction of both left ventricular function and myocardial oxygen metabolism LVEDP rose to 32 cm H_2O and LV dP/dt max fell to about 30 per cent of time 0 values Coronary flow fell from 17 2 (± 0 6 S E) to 11 5 (± 0 9 S E) ml per minute and myocardial O_2 availability declined from 12 14 (± 1 66 S E) to 8 18 (± 0 87 S E) ml per minute per 100 Gm HW MVo_2 and O_2 extraction also fell significantly (Table II)

Six animals demonstrated a progressive reduction of ventricular function with sustained hypotension but a level of severity comparable to the above was not reached until about 1 hour of shock (55 2 ± 2 8 S E minutes) The mean values for LVEDP and LV dP/dt max at time 0 were 5 5 cm H_2O and 1 208 mm Hg per second respectively Coronary flow was 15 9 ml per minute and myocardial O_2 availability was 12 9 ml per minute 100 Gm HW Extraction was 76 12 per cent and MVo_2 averaged 9 62 ml per minute per 100 Gm HW After 30 minutes however LVEDP rose to 9 0 cm H_2O and LV dP/dt max, coronary flow myocardial O_2 extraction and MVo_2 were all somewhat reduced Within 1 hour of sustained hypotension the animals showed marked deterioration of left ventricular function LVEDP increased to 22 6 cm H_2O ($p < 0.01$) and LV dP/dt max fell to 536 mm Hg per second ($p < 0.01$) Coronary flow fell to 11 5 ml per minute and myocardial O_2 availability was reduced to 9 45 ml per minute per 100 Gm HW Concomitantly O_2 extraction and MVo_2 were markedly decreased to 56 per cent ($p < 0.05$) and 5 28 ml per minute per 100 Gm HW ($p < 0.01$) respectively

Two animals (Table II) showed no significant reduction of left ventricular function during 90 minutes of sustained hypotension as indicated by little change in LVEDP or dP/dt max Coronary flow showed a small progressive decrease But myocardial O_2 availability extraction and MVo_2 were unchanged over the 1½ hour period It may be noted that the arterial oxygen content and hematocrit in these animals were significantly higher than in those which developed mechanical failure (Table II)

Relationship of ventricular performance to myocardial oxygen availability The data were further analyzed by examining relationship

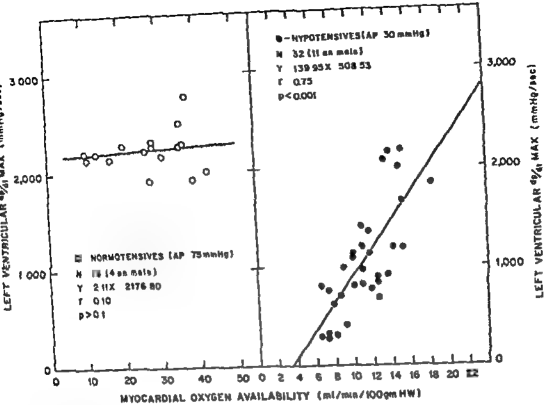

Fig 2 Relationship of myocardial oxygen availability to maximal rate of rise of left ventricular pressure (LV dP/dt max) Closed circles = shock animals (right panel) open circles = control animals (left panel) See text for further description

between the left ventricular dP/dt max and myocardial O availability Values from the 11 shock cats (32 observations) are plotted in the right hand panel of Fig 2 The calculated linear regression line is also shown A highly significant correlation between LV dP/dt max and O availability was found (r = 0 75 p < 0 01) indicating that ventricular performance in these preparations was closely linked with oxygen availability during shock In sharp contrast no correlation was found between LV dP/dt max and myocardial O availability in normotensive controls (r = 0 1 p > 0 1) The data from 16 observations are shown in the left hand panel of Fig 2

Relationship of aortic pressure (coronary perfusion pressure) to ventricular mechanics and oxygen metabolism The above findings suggest a close relationship between coronary flow a major determinant of myocardial O availability and changes in left ventricular performance and myocardial oxygen metabolism in hemorrhagic shock This point is further demonstrated by the data from two animals shown in Table III With *aortic flow* and heart rate held constant oxygen delivery to the myocardium was reduced by sequentially lowering coronary perfusion pressure There was a progressive reduction of coronary flow accompanied by increasing oxygen extraction LV dP/dt max also fell probably as a *mechanical consequence of lowering ventricular* afterloading However in both animals LVEDP and MVo_2 changed little until aortic pressure was reduced to 30 mm Hg and myocardial O_2 availability fell to about 11 ml per minute per 100 Gm HW Under these conditions LVEDP rose sharply to about 10 cm H O and dP/dt max declined further Improvement of myocardial function and oxygen metabolism was observed in each preparation upon re elevation of aortic pressure This increase in mechanical performance paralleled an increase of coronary flow and myocardial O_2 availability

Discussion

Previous work from this laboratory has shown that sustained hemorrhagic hypotension (AP = 30 mm Hg) accompanied by periodic episodes of hypoxemia leads to a more rapid deterioration of

Table III Effects of aortic pressure (coronary perfusion pressure) on ventricular mechanics and oxygen metabolism

AP	*CF*	*Myoc O_2 ext*	*MVO*	*Myoc O_2 avail*	*LVEDP*	*LV dP/dt max*
Cat No 21	body weight 3.6 Kg		heart rate 226 b p m	aortic flow 235 ml/min		hematocrit [illegible]
100	22	67.04	10.27	15.35	4.0	[illegible]
75	20	73.03	10.07	15.10	3.5	[illegible]
50	17	81.60	10.87	13.32	4.0	1 103
30	14	80.87	8.95	11.07	10.0	[illegible]
50	20	72.50	10.63	14.66	4.5	[illegible]
Cat No 23	body weight 3.2 Kg		heart rate 222 b p m	aortic flow 250 ml/min		hematocrit [illegible]
75	20	48.09	10.34	21.46	3.0	3 158
35	14	69.88	10.57	15.16	3.0	1 658
30	9	82.90	9.43	11.42	9.5	1 188
70	30	41.47	10.64	32.80	3.5	3 504

Abbreviations same as in Table I
b p m = beats per minute

myocardial function than when Pa_{O_2} is kept normal. This study also demonstrated that cardiac deterioration during severe hypotension may be delayed by employing less severe hypoxia observing the critical Pa_{O_2}. These observations supported *the concept of cumulative hypoxic* tissue damage in shock and suggested that oxygen availability is a primary factor in determining reversibility of myocardial depression. The present study was undertaken to obtain more direct evidence for the relationship between these two events.

Myocardial oxygen availability may be simply expressed as the product of coronary blood flow and arterial oxygen concentration. Under normal conditions the amount of oxygen that can be carried by plasma in blood is very small, about 0.3 volume per cent. Therefore the oxygen carrying capacity of blood is largely dependent on the hematocrit ratio. The importance of the hematocrit to susceptibility to irreversible hemorrhagic shock has been demonstrated by Crowell and associates.[18] They showed that in dogs the time required for the development of irreversible shock was proportional to the hematocrit in the range of 12 to 35 per cent. However above 35 per cent the likelihood for survival of the animal was proportionally decreased. They suggested that this might be due to an increase of "apparent viscosity" in the blood which further reduces blood flow to the tissues. The optimum hematocrit in anesthetized dogs for surviving hemorrhagic shock was found to be 30 to 35 per cent.[19] Similar conclusions were reached by Chien and associates.[9] The relationship of coronary perfusion pressure and left ventricular function to hematocrit ratio has also been demonstrated by Beneke and associates.[1]

Earlier studies of Sarnoff and associates[3] presented evidence that insufficient coronary flow *is* a major cause for myocardial failure in late hemorrhagic shock. Myocardial depression could be reversed by augmenting coronary flow with an external pump or pharmacologically induced vasodilatation with Arminc.[2] Recent work of Bethea and associates also demonstrated that cardiac deterioration during hemorrhagic hypotension could be reduced by pretreatment of animals with the coronary vasodilator, dipyridamole (0.15 mg per kilogram). They suggested that since dipyridamole had no direct effect on myocardial contractility,[1] it must exert a protective action through its effect on coronary blood flow. This is consistent with earlier work from this laboratory[1] in which animals were subjected to hemorrhagic shock (30 mm Hg) but coronary perfusion pressure was maintained at normal levels (100 mm Hg) to provide adequate coronary flow. After 2 hours of shock severe metabolic acidosis developed but ventricular function did not differ from control animals. Those with shock level coronary perfusion pressure showed progressive reduction in contractility to about 45 per cent of control.

The observations cited above suggest that the appearance of left ventricular failure in hemorrhagic shock may be related to an inadequate myocardial oxygen supply. This concept is con

sistent with our present findings During the course of sustained hypotension animals with the highest arterial oxygen concentration and hematocrit were most resistant to changes in cardiac performance or oxygen metabolism (Table II) Myocardial O_2 availability remained *relatively* high (approximately 13 ml *per minute per* 100 Gm HW) On the other hand in animals where myocardial O_2 availability fell below *10 ml per* minute per 100 Gm HW cardiac failure constantly appeared and thus was accompanied by a reduction in myocardial O_2 extraction and consumption (Table II) Moreover two animals with marginal O_2 delivery to the myocardium (10 6 ± 0 7 S E ml per minute per 100 Gm HW) prior to hemorrhage were *unable to tolerate* hypotension and died with ventricular fibrillation shortly after the onset of shock The close relationship between ventricular function and myocardial O_2 availability during hemorrhagic shock is clear from the data shown in Fig 2 As myocardial O_2 availability diminished there was a *concomitant* reduction of left ventricular dP/dt max Regression analysis indicates a highly significant association These findings may be compared with control animals (AP = 75 mm Hg) with equally low hematocrit values (Table I) No significant changes in myocardial O_2 metabolism or performance occurred over the 90 minute period It should be noted that average O_2 delivery to the myocardium remained well above 10 ml *per* minute *per* 100 *Gm* HW in these animals

The progressive reduction of myocardial O_2 availability during shock was primarily consequent to a reduction of coronary flow This was unexpected since metabolic acidosis also appeared (Table II) and would presumably contribute to dilatation *of the coronary* tree Indeed most studies have reported a *fall of coronary* resistance during hemorrhagic hypotension Others however have found in both isolated heart and intact preparations increased resistance as in the present study The reason remains unclear Some have suggested that it may relate to reduced myocardial oxygen demand or increased centrally *mediated* alpha adrenergic activity

It would seem unlikely that the decrease in MVo and myocardial O_2 extraction associated with *deterioration* of ventricular function can be attributed merely to a reduction in contractility and decreased oxygen demand Ventricular wall tension must have increased significantly with the appearance of cardiac failure as reflected by the elevation of LVEDP in these experiments (Table II) This would be expected to increase the O_2 *requirements of the myocardium A more likely* explanation may be the development of a progressive shift in metabolic pathways toward anaerobic metabolism followed by the inability of myocardial tissues to extract oxygen Thus the decrease in MVo_2 would appear most reasonably relatable to the appearance of a defect in myocardial *cellular* metabolism These conclusions are consistent with the findings of Edwards and associates and *others* Evidence *for myocardial structural alterations* which appear in the course *of* hemorrhagic *shock* supports this concept

Recent studies have shown that following severe hemorrhage and prior *to* biochemical manifestations for myocardial hypoxia preferential substrate utilization of myocardium *shifts* from free fatty acid to carbohydrate and that this shift precedes any functional deterioration This change of preference was attributed to a limitation *of* O_2 *supply and thought to contribute to the* subsequent *irreversible deterioration of circulatory* function

The pathophysiological changes observed in experimental hemorrhagic shock are complex and likely depend to some extent on the protocol and experimental conditions Our results demonstrate a close relationship between mechanical function and oxygen *metabolism* of the heart during the course of hemorrhagic shock in the cat model When myocardial O_2 availability fell below 10 ml per minute per 100 Gm HW during shock *cardiac* failure constantly appeared and was accompanied by a reduction in myocardial O_2 extraction and consumption The importance of O_2 availability in determining cardiac function has been established but it is not certain from these data whether reduced O_2 metabolism is the cause or the result of destruction *of* myocardial metabolic pathways

Summary

The relationships between left ventricular function and myocardial O_2 availability and metabolism were studied in cats with hemorrhagic shock (AP = 30 mm Hg) with the use of a right heart bypass *preparation* Aortic flow and

Table III Effects of aortic pressure (coronary perfusion pressure) on ventricular mechanics and ox$_y$ metabolism

AP	CF	Myoc O_2 ext	MVO	Myoc O_2 avail	LVEDP	LV dP/dt max
Cat No 21	body weight 3 6 Kg		heart rate 226 b p m *	aortic flow 235 ml /min		hematocrit [illegible]
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75	20	73 03	10 07	15 10	3 5	1 641
50	17	81 60	10 87	13 32	4 0	1 103
30	14	80 87	8 95	11 07	10 0	88[illegible]
50	20	72 50	10 63	14 66	4 5	1 373
Cat No 23	body weight 3 2 Kg		heart rate 222 b p m	aortic flow [illegible]50 ml/min		hematocrit [illegible]
75	20	48 09	10 34	21 46	3 0	3 159
35	14	69 88	10 57	15 16	3 0	1 658
30	9	82 90	9 43	11 42	9 5	1 188
70	30	41 47	10 64	32 80	3 [illegible]	3 504

Abbreviations same as in Table I
b p m = beats per minute

myocardial function than when Pa_{O} is kept normal This study also demonstrated that cardiac deterioration during severe hypotension may be delayed by employing less severe hypoxia observing the critical Pa_{O} These observations supported the concept of cumulative hypoxic tissue damage in shock and suggested that oxygen availability is a primary factor in determining reversibility of myocardial depression The present study was undertaken to obtain more direct evidence for the relationship between these two events

Myocardial oxygen availability may be simply expressed as the product of coronary blood flow and arterial oxygen concentration Under normal conditions the amount of oxygen that can be carried by plasma in blood is very small about 0 3 volume per cent Therefore, the oxygen carrying capacity of blood is largely dependent on the hematocrit ratio The importance of the hematocrit to susceptibility to irreversible hemorrhagic shock has been demonstrated by Crowell and associates[18] They showed that in dogs the time required for the development of irreversible shock was proportional to the hematocrit in the range of 12 to 35 per cent However, above 35 per cent the likelihood for survival of the animal was proportionally decreased They suggested that this might be due to an increase of apparent viscosity in the blood which further reduces blood flow to the tissues The optimum hematocrit in anesthetized dogs for surviving hemorrhagic shock was found to be 30 to 35 per cent[19] Similar conclusions were reached by Chien and associates[8] The relationship of coronary perfusi[illegible] pressure and left ventricular function to hemat[illegible] crit ratio has also been demonstrated by Benek[illegible] and associates[1]

Earlier studies of Sarnoff and associates p[illegible] sented evidence that insufficient coronary flow a major cause for myocardial failure in la[illegible] hemorrhagic shock Myocardial depression cou[illegible] be reversed by augmenting coronary flow with external pump or pharmacologically induc[illegible] vasodilatation with Armine Recent work Bethea and associates[4] also demonstrated th[illegible] cardiac deterioration during hemorrhagic hyp[illegible] tension could be reduced by pretreatment animals with the coronary vasodilator dipyrid[illegible] mole (0 15 mg per kilogram) They suggested that since dipyridamole had no direct effect on myocardial contractility[1] it must exert a protective action through its effect on coronary blood flow This is consistent with earlier work from this laboratory[11] in which animals were subjected to hemorrhagic shock (30 mm Hg) but coronary perfusion pressure was maintained at normal levels (100 mm Hg) to provide adequate coronary flow After 2 hours of shock severe metabolic acidosis developed but ventricular function did not differ from control animals Those with shock level coronary perfusion pressure showed progressive reduction in contractility to about 45 per cent of control

The observations cited above suggest that the appearance of left ventricular failure in hemorrhagic shock may be related to an inadequate myocardial oxygen supply This concept is con

sistent with our present findings During the course of sustained hypotension animals with the highest arterial oxygen concentration and hematocrit were most resistant to changes in cardiac performance or oxygen metabolism (*Table II*) Myocardial O_2 availability remained relatively high (approximately 13 ml per minute per 100 Gm HW) On the other hand in animals where myocardial O availability fell below 10 ml per minute per 100 Gm HW cardiac failure constantly appeared and this was accompanied by a reduction in myocardial O_2 extraction and consumption (Table II) Moreover two animals with marginal O delivery to the myocardium ($10 6 \pm 0 7$ S E ml per minute per 100 Gm HW) prior to hemorrhage were unable to tolerate hypotension and died with ventricular fibrillation shortly after the onset of shock The close relationship between ventricular function and myocardial O availability during hemorrhagic shock is clear from the data shown in Fig 2 As myocardial O_2 availability diminished there was a concomitant reduction of left ventricular dP/dt max Regression analysis indicates a highly significant association These findings may be compared with control animals (AP = 7o mm Hg) with equally low hematocrit values (Table I) No significant changes in myocardial O metabolism or performance occurred over the 90 minute period It should be noted that average O delivery to the myocardium remained well above 10 ml per minute per 100 Gm HW in these animals

The progressive reduction of myocardial O availability during shock was primarily consequent to a reduction of coronary flow This was unexpected since metabolic acidosis also appeared (Table II) and would presumably contribute to dilatation of the coronary tree Indeed most studies have reported a fall of coronary resistance during hemorrhagic hypotension Others however have found in both isolated heart and intact preparations increased resistance as in the present study The reason remains unclear Some have suggested that it may relate to reduced myocardial oxygen demand or increased centrally mediated alpha adrenergic activity

It would seem unlikely that the decrease in MVo and myocardial O extraction associated with deterioration of ventricular function can be attributed merely to a reduction in contractility and decreased oxygen demand Ventricular wall tension must have increased significantly with the appearance of cardiac failure as reflected by the elevation of LVEDP in these experiments (Table II) This would be expected to increase the O_2 requirements of the myocardium A more likely explanation may be the development of a progressive shift in metabolic pathways toward anaerobic metabolism followed by the inability of myocardial tissues to extract oxygen Thus the decrease in MVo_2 would appear most reasonably relatable to the appearance of a defect in myocardial cellular metabolism These conclusions are consistent with the findings of Edwards and associates and others [4, 5 ... 11] Evidence for myocardial structural alterations which appear in the course of hemorrhagic shock supports this concept [1]

Recent studies[1] have shown that following severe hemorrhage and prior to biochemical manifestations for myocardial hypoxia preferential substrate utilization of myocardium shifts from free fatty acid to carbohydrate and that this shift precedes any functional deterioration [3] This change of preference was attributed to a limitation of O_2 supply and thought to contribute to the subsequent irreversible deterioration of circulatory function [4]

The pathophysiological changes observed in experimental hemorrhagic shock are complex and likely depend to some extent on the protocol and experimental conditions Our results demonstrate a close relationship between mechanical function and oxygen metabolism of the heart during the course of hemorrhagic shock in the cat model When myocardial O_2 availability fell below 10 ml per minute per 100 Gm HW during shock cardiac failure constantly appeared and was accompanied by a reduction in myocardial O_2 extraction and consumption The importance of O_2 availability in determining cardiac function has been established but it is not certain from these data whether reduced O metabolism is the cause or the result of destruction of myocardial metabolic pathways

Summary

The relationships between left ventricular function and myocardial O availability and metabolism were studied in cats with hemorrhagic shock (AP = 30 mm Hg) with the use of a right heart bypass preparation Aortic flow and

Table III Effects of aortic pressure (coronary perfusion pressure) on ventricular mechanics and oxygen metabolism

AP	CF	Myoc O ext	MVO	Myoc O_2 avail	LVEDP	LV dP/dt max
Cat No 21	body weight 3 6 Kg		heart rate 226 b p m	aortic flow 235 ml /min		hematocrit %
100	22	67 04	10 27	15 35	4 0	2 219
75	20	73 03	10 07	15 10	3 5	1 671
50	17	81 60	10 87	13 32	4 0	1 103
30	14	80 87	8 95	11 07	10 0	882
50	20	72 50	10 63	14 66	4 5	1 393
Cat No 23	body weight 3 2 Kg		heart rate 222 b p m	aortic flow 250 ml/min		hematocrit %
75	20	48 09	10 34	21 46	3 0	3 158
35	14	69 88	10 57	15 16	3 0	1 658
30	[illegible]	82 90	9 43	11 42	9 5	1 158
70	30	41 47	10 64	32 80	3 5	3 504

Abbreviations same as in Table I
b p m = beats per minute

myocardial function than when Pa_{O_2} is kept normal This study also demonstrated that cardiac deterioration during severe hypotension may be delayed by employing less severe hypoxia observing the critical Pa_{O_2} These observations supported the concept of cumulative hypoxic tissue damage in shock and suggested that oxygen availability is a primary factor in determining reversibility of myocardial depression The present study was undertaken to obtain more direct evidence for the relationship between these two events

Myocardial oxygen availability may be simply expressed as the product of coronary blood flow and arterial oxygen concentration Under normal conditions the amount of oxygen that can be carried by plasma in blood is very small about 0 3 volume per cent Therefore the oxygen carrying capacity of blood is largely dependent on the hematocrit ratio The importance of the hematocrit to susceptibility to irreversible hemorrhagic shock has been demonstrated by Crowell and associates[18] They showed that in dogs the time required for the development of irreversible shock was proportional to the hematocrit in the range of 12 to 35 per cent However, above 35 per cent the likelihood for survival of the animal was proportionally decreased They suggested that this might be due to an increase of apparent viscosity in the blood which further reduces blood flow to the tissues The optimum hematocrit in anesthetized dogs for surviving hemorrhagic shock was found to be 30 to 35 per cent[19] Similar conclusions were reached by Chien and associates The relationship of coronary perfusion pressure and left ventricular function to hematocrit ratio has also been demonstrated by Beneken and associates[1]

Earlier studies of Sarnoff and associates presented evidence that insufficient coronary flow is a major cause for myocardial failure in late hemorrhagic shock Myocardial depression could be reversed by augmenting coronary flow with an external pump or pharmacologically induced vasodilatation with Armine Recent work of Bethea and associates also demonstrated that cardiac deterioration during hemorrhagic hypotension could be reduced by pretreatment of animals with the coronary vasodilator dipyridamole (0 15 mg per kilogram) They suggested that since dipyridamole had no direct effect on myocardial contractility[1] it must exert a protective action through its effect on coronary blood flow This is consistent with earlier work from this laboratory[1] in which animals were subjected to hemorrhagic shock (30 mm Hg) but coronary perfusion pressure was maintained at normal levels (100 mm Hg) to provide adequate coronary flow After 2 hours of shock severe metabolic acidosis developed but ventricular function did not differ from control animals Those with shock level coronary perfusion pressure showed progressive reduction in contractility to about 45 per cent of control

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fun tional capacity of mito hondria in hemorrhagic shock, Surgery 68 40 19 0
30 Cowsert M K Carrier II and Crowell J W The effect of hemorrhagic hock on blood uric acid level Can J Physiol Pharmacol 44 661 1966.
31 McShan W II Potter V R Goldman A Sh pley F A and Meyer R K Biological energy tran formations during shock as shown by blood chemistry Am J Physiol 145 93 1945
32 Chang J and Hackel D B Comparati e study of myocardial lesions in hemorrhagic shock, Lab Invest 28 641 19 3
33 K jiha a H Hara H Seyama S Iijima S and Yoshidoa Light and ele tro n microscopic observations of the myocardium of dogs in hemorrhagic shock Acta Pathol Jap 23 315 19 3
34 Martin A. M and Hackel D B The myocardium of the dog in hemorrhagic shock A Hi tochemical study Lab Invest 12 77 1963
35 Spitzer J J Bechtel A A Archer L T Black M R and Hinshaw L B Myocardial substrate utilization in dogs following endotoxin admini tration Am J Physiol 227 132 19 4
36 Spitzer J J and Spitzer J A Myocardial metaboli m in dogs during hemorrhagic shock, Am. J Physiol. 222 101 1972
37 Wiener R and Spitzer J J Lacta e metaboli m following severe hemorrhage in the conscious dog Am J Physiol 227 58 19 4
38 Wiener R and Spitzer J J Glucose metabolism following severe hemorrhage in the conscious dog Am J Physiol 227 63 19 4

heart rate were held constant Oxygen carrying capacity was reduced by diluting donor blood with an equal volume of 5 per cent glucose in saline Oxygen availability was estimated as the product of arterial O_2 content and coronary blood flow All shock animals showed a progressive metabolic acidemia with time and a fall in coronary flow concomitantly Four control animals (AP = 75 mm Hg) as well as two shock animals with high arterial oxygen content and hematocrit showed no significant changes in myocardial O metabolism or performance over a period of 90 minutes Nine shock animals with reduced hematocrit demonstrated a progressive reduction in ventricular function myocardial O metabolism and O_2 availability As O availability fell below 10 ml per minute per 100 Gm of heart weight cardiac failure uniformly appeared and was accompanied by a reduction in O extraction and consumption The correlation between left ventricular dP/dt max and O availability was highly significant ($r = 0.75$ $p < 0.01$) in shock animals but not in controls Thus a close relationship between myocardial O metabolism and function during the course of hemorrhagic shock has been demonstrated Reduced myocardial O_2 availability is directly linked with the appearance of cardiac failure

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REFERENCES

1 Wiggers C J and Werle J M Cardiac and peripheral resistance factors as determinants of circulatory failure in hemorrhagic shock Am J Physiol 136 421 1942
2 Sarnoff S J Case R B Waithe P E and Isaacs J P Insufficient coronary flow and myocardial failure as a complicating factor in later hemorrhagic shock Am J Physiol 176 439 1954
3 Crowell J W and Guyton A C Evidence favoring a cardiac mechanism in irreversible hemorrhagic shock Am J Physiol 201 893 1961
4 Hinshaw L B Archer T L Greenfield L J and Guenter C A Effect of endotoxin on myocardial hemodynamics performance and metabolism Am J Physiol 221 504 1971
5 Jones C E Bethea H L Smith E E and Crowell J W Effect of a coronary vasodilator on the development of irreversible hemorrhagic shock Surgery 68 356 1970
6 Opdyke D F and Foreman R C A study of coronary flow under conditions of hemorrhagic hypotension and shock Am J Physiol 148 726 1947
7 Mazor A M and Rogel S Cardiac aspects of shock Effects of an ischemic body on a non ischemic heart Ann Surg 178 128 1973
8 Lefer A M Blood borne humoral factors in the pathophysiology of circulatory shock Circ Res 32 129 1973
9 Claviano V V and Coleman B Myocardial depletion of norepinephrine in hemorrhagic hypotension Proc Soc Exp Biol Med 107 761 1961
10 Bond R F Manning E A Gonzalez N M Gonzalez R R and Becker V E Myocardial and skeletal muscle responses to hemorrhage and shock during adrenergic blockade Am J Physiol 225 247 1973
11 Rother C F Heart failure and fluid loss in hemorrhagic shock Fed Proc 29 1854 1970
12 Siegel H W and Downing S E Reduction of left ventricular contractility during acute hemorrhagic shock Am J Physiol 218 772 1970
13 Siegel H W and Downing S E Contributions of coronary perfusion pressure metabolic acidosis and adrenergic factors to the reduction of myocardial contractility during hemorrhagic shock in the cat Circ Res 27 875 1970
14 Lee J C and Downing S E Critical oxygen tension and left ventricular performance during shock Am J Physiol 226 9 1974
15 Roughton F J W and Scholander P F Micro gasometric estimation of the blood gases I Oxygen J Biol Chem 148 542 1943
16 Hackel D B Goodale W T and Kleinerman J Effects of hypoxia on myocardial metabolism of intact dogs Circ Res 2 169 1954
17 Lewis A F Biostatistics New York 1966 Reinhold Publishing Company
18 Crowell J W Bounds S H and Johnson W W Effect of varying the hematocrit ratio on the susceptibility to hemorrhagic shock Am J Physiol 192 1 1958
19 Crowell J W Oxygen transport in the hypotensive state Fed Proc 29 1848 1970
20 Chien S Dellenback R J Usami S Burton D A Gustavson P F and Magazinovic V Blood volume hemodynamic and metabolic changes in hemorrhagic shock in normal and splenectomized dog Am J Physiol 225 866 1973
21 Beneken J E W Guyton A C and Sagawa K Coronary perfusion pressure and left ventricular function Pflugers Arch 305 76 1969
22 Bethea H L Jones C E and Crowell J W Effect of pharmacologic coronary flow augmentation on cardiac function in hypotension Am J Physiol 222 95 1972
23 West J W Bellet S Manzoli U C and Muller O F Effects of persantin (RA8) a new coronary vasodilator on coronary blood flow and cardiac dynamics in the dog Circ Res 10 35 1961
24 Edwards W S Siegel A and Bing R J Studies on myocardial metabolism III Coronary blood flow myocardial oxygen consumption and carbohydrate metabolism in experimental hemorrhagic shock J Clin Invest 33 1646 1954
25 Hackel D B and Goodale W T Effects of hemorrhagic shock on the heart and circulation of intact dogs Circulation 11 628 1955
26 Horvath S M Farrand E A and Hutt B K Cardiac dynamics and coronary blood flow consequent to acute hemorrhage Am J Cardiol 2 357 1958
27 Granata L Huvos A Pasque A and Gregg D E Left coronary hemodynamics during hemorrhagic hypotension and shock Am J Physiol 216 1583 1969
28 Vatner S F Effects of hemorrhage on regional blood flow distribution in dogs and primates J Clin Invest 54 225 1974
29 Baue A L and Sayeed M M Alterations in the

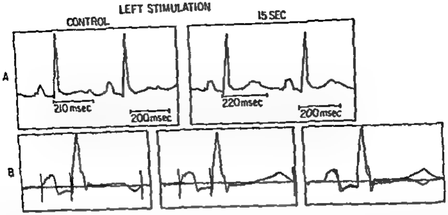

Fig 1 Effects of brief stimulation of the left anterior ansa on the QT interval in a vertical ECG lead in two dogs. Records in the upper panels (*A*) are before and 15 seconds after stimulation for 2 seconds with 2 msec square wave pulses at 12 Hz and 2 volts. The time scale is indicated by 200 msec intervals in the lower right corner of each panel. Duration of the QT interval increased from 210 to 220 msec as a result of nerve stimulation. Records shown in the lower panels (*B*) are signal averaged from 10 complexes before and beginning 3 seconds after stimulation of the left stellate ganglion for 2 seconds with pulses of 4 msec duration at 12 Hz and [illegible] volts. Pre and poststimulation records are shown separately in the first two panels and superimposed in the last panel. The QT prolongation evident in the poststimulation record is 27 msec with the time scale used for the averaged wave forms.

to alter ECG wave form after 1 to 3 seconds of stimulation was determined. Since the measure of stimulus effectiveness was based on ECG wave form the intensity was arbitrarily expressed as volts rather than current. Prolonged nerve stimulus effectiveness was also assessed by the occurrence of ECG wave form changes. ECGs were recorded at paper speeds of 50 to 400 mm per second. QT intervals were measured in milliseconds and those prior to and at intervals after the various interventions compared. In some experiments ECGs were recorded on magnetic tape and signal averaging of 8 to 10 complexes to reduce ambient noise and individual cycle wave form variations was carried out prior to QT interval measurements.

Results

Both prolongation and reduction of the QT interval were produced by sympathetic nerve stimulation and by catecholamine injection. Brief nerve stimulation or rapid catecholamine injection was followed by transient prolongation of the QT interval. Slow catecholamine infusion or prolonged sympathetic nerve stimulation resulted in no alteration or reduction of the QT interval.

Brief nerve stimulation. *One to 3 second stimu*lation of the left stellate ganglion, left anterior ansa, or the left ventromedial cardiac nerve was carried out in eight experiments. Stimulus intensity and frequency were adjusted to result in ECG wave form changes and varied from 12 to 16 Hz and 1 to 30 volts in individual experiments. Prolongation of the QT interval in the vertical lead occurred in all these experiments. The magnitude of prolongation varied from 10 to 30 msec and duration of prolongation from a few seconds to several minutes. The time of occurrence of QT prolongation varied, sometimes being evident before the end of a 3 second period of nerve stimulation but usually occurring in the 10 to 30 second period after stimulation. Harris and co-workers[3] found that arrhythmias following 10 second stimulation of the ansa subclavia in the presence of coronary occlusion in dogs usually had their onset 10 to 30 seconds after stimulation, suggesting a relationship between the period of QT prolongation demonstrated in their study and arrhythmias. In all but one experiment the QT interval decreased to its control value gradually over a period of seconds to minutes. In the exception, QT prolongation was evident at the end of a 3 second period of *stimulation of the left* anterior ansa, *increased* to a maximum at 4 seconds after stimulation, and then transiently shortened below the control value at 20 seconds before returning to the control value by 30 *seconds following* stimulation. Examples of QT prolongation following brief left sympathetic

Adrenergic effects on the QT interval of the electrocardiogram

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Salt Lake City Utah

Prolongation of the QT interval in the electrocardiogram (ECG) occurs in several states in which the incidence of cardiac arrhythmias and sudden death is high These include the idiopathic prolonged QT interval syndromes quinidine and various other drug intoxications, and hypokalemia Such associations demonstrate that QT interval prolongation sometimes identifies cardiac conditions susceptible to serious arrhythmias but detailed mechanisms responsible for the associations have not been determined

It has been shown that the relation of QT interval and ventricular recovery time is complex in that some agencies which alter recovery time result in paradoxical effects on the interval[1-4] One of these agencies is left stellate ganglion stimulation in the dog, which frequently results in prolongation of the QT interval, although refractory periods are actually reduced in the innervated area[1-4] This suggests that prolongation of the QT interval may sometimes reflect a cardiac state with greater than normal disparity of recovery times rather than one in which simply prolonged recovery is present The degree of inequality of recovery times in cardiac muscle has been extensively documented to be a factor in arrhythmia susceptibility[5-12] These considerations suggest that the utility of the QT interval as an indicator of cardiac states vulnerable to arrhythmias should be further investigated

The present study was undertaken to elucidate mechanisms operating in the reflection of ventricular recovery by the QT interval Findings confirmed frequent paradoxical behavior of the QT interval in relation to alterations of recovery and furnished new information concerning mechanisms of this behavior Findings also suggested that states in which paradoxical QT interval behavior occurs are ones with increased disparity of recovery and by operation of that mechanism are states of enhanced vulnerability to arrhythmias

Materials and methods

Experiments were performed on nine dogs anesthetized with pentobarbital, 30 mg per kilogram The thorax was opened in the midline and the heart exposed by pericardial incision A vertical ECG lead from electrodes on the left hind leg and neck was obtained All ECG observations were made with the heart paced from a bipolar electrode on the right atrium or from various ventricular sites The sinus node was crushed and the heart driven at a rate exceeding that of spontaneous rhythm

Ventricular recovery was altered by electrical stimulation of cardiac sympathetic nerves or by the intravenous injection of epinephrine or norepinephrine In various experiments, stimulation of the left stellate ganglion, left anterior ansa subclavia left ventromedical cardiac nerve right stellate ganglion, or right anterior ansa subclavia were carried out In the experiments reported nerves were intact, however previous studies with barbiturate anesthetized dogs showed similar ECG effects of stimulating intact and decentralized nerves[1] Those findings do not suggest that stimulation of both afferent and efferent fibers is not capable of producing both direct and reflex effects but only that reflex effects were not a significant factor in the experiments reported here The effectiveness of brief nerve stimulation was assessed by preliminary observations in each experiment in which stimulus intensity necessar

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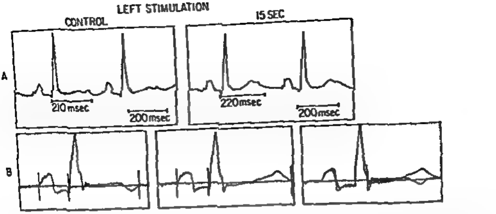

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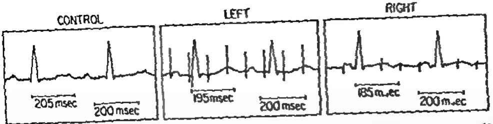

Fig 3 Records from one experiment showing reduction of the QT interval during prolonged stimulation of left and of right anterior ansae Stimulation of the left ansa consisted of 2 msec pulses at 12 Hz and 4 volts for 5 minutes. The record shown was obtained after 2 minutes of stimulation and further QT interval reduction did not occur with continued stimulation The record shown during right anterior ansa stimulation was obtained after 1 minute of stimulation with 2 msec pulses at [illegible] Hz and 2 volts and no further QT interval change occurred during 5 minutes of stimulation

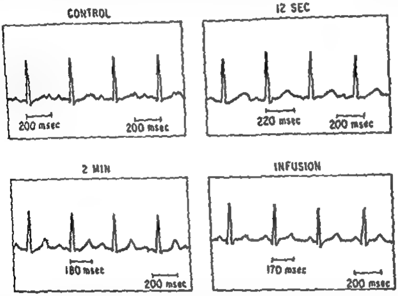

Fig 4 Effects of rapid injection of epinephrine 0 25 mg in 1 c c solution are shown at 12 seconds and [illegible] minutes after the injection At 12 seconds QT duration is increased by 0 msec compared to the control record and by 2 minutes has decreased by a similar amount The last panel titled infusion " is from the same experiment and shows 30 msec decrease in the QT interval during infusion of epinephrine 1 mg in 500 c c of 5 per cent dextrose in water The infusion rate was adjusted to result in gradual alteration of T wave form and the record shown was obtained 3 minutes after initiating the infusion

experiment is illustrated in Fig 3 In that animal stimulation of the left anterior ansa with 2 msec pulses at 12 Hz and 4 volts reduced the QT interval by 10 msec after 2 minutes and further reduction did not occur with continued stimulation for 5 minutes In the same experiment stimulation of the right anterior ansa with 2 msec pulses at 12 Hz and 2 volts reduced the QT interval by 20 msec after 1 minute and no further reduction occurred with 5 minutes of nerve stimulation In one of the experiments not illustrated stimulation of the right anterior ansa reduced the QT interval by 20 msec after 3 minutes but not after 1 or 2 minutes of stimulation In the other two experiments with prolonged nerve stimulation only the effects of left stellate stimulation were determined and QT interval was evaluated during early as well as late portions of the stimulation period In both experiments QT prolongation occurred during the first 10 to 20 seconds after initiation of stimulation and in both instances was followed by QT reduction with maximum values of 15 and 20 msec during the first 2 minutes of stimulation Average QT reduction with prolonged stimulation of left sided nerves was 11 msec for the four experiments in which this observation was made Both experiments in which the effects of prolonged right

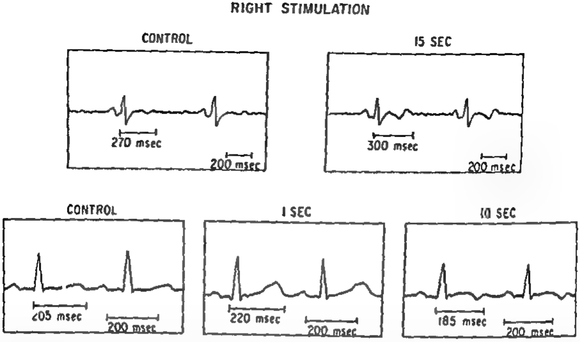

Fig 2 Effects of right anterior ansa stimulation on the QT interval of a vertical ECG lead in two dogs The upper panels show records before and 15 seconds after stimulation of the right anterior ansa with 2 msec pulses at 12 Hz and 20 volts Nerve stimulation resulted in T wave form changes and 30 msec QT prolongation The lower three panels show pre and poststimulation records from an experiment in which the right anterior ansa was stimulated for 3 seconds with 2 msec square wave pulses at 12 Hz and 4 volts Prolongation of the QT interval illustrated at 1 second was evident for 4 seconds after nerve stimulation and by 10 seconds after stimulation was reduced below the prestimulation duration

nerve stimulation are shown in Fig 1 The records shown in part *A* are from an experiment in which the left anterior ansa was stimulated for 2 seconds with 12 Hz 2 msec pulses at 2 volts The post stimulation record shown was obtained 15 seconds after completion of nerve stimulation and shows the T wave form changes and QT interval prolongation following left stellate stimulation for 2 seconds with 4 msec pulses at 12 Hz and 2 volts In another experiment illustrated in part *B* of Fig 1, QT prolongation was evident during a period 3 to 10 seconds following nerve stimulation and 10 complexes from this period were signal averaged to reduce noise and permit more accurate assessment of QT interval duration The records shown are the averaged complexes before and after stellate stimulation and are shown separately in the first two panels and superim posed in the last one The QT prolongation evident measured 27 msec with the time scale used for the average complexes

One to 3 msec stimulation of the right stellate ganglion or right anterior ansa was carried out in four experiments In two of these, tachycardia exceeding the driven rate prevented valid obser vations of the QT interval in the immediate post-nerve stimulation period In the other expe riments which are illustrated in Fig 2 transient QT interval prolongation occurred In the experi ment represented in the upper panels QT prolon gation was evident by 15 seconds after 3 seconds of nerve stimulation with 2 msec pulses at 12 Hz and 20 volts and prolongation persisted for another 30 seconds Records in the lower panels illustrate QT interval prolongation at 1 second after stimulation of the right anterior ansa with 12 Hz 2 msec pulses of 4 volts for 3 seconds The QT interval prolongation was evident immediate ly after stimulation persisted for 4 seconds then decreased to a minimum value at 10 seconds and returned to control value during several seconds The records in the lower panels of Fig 2 show a strikingly biphasic effect on T wave form with the early change being increased T wave amplitude and later changes resulting in T wave inversion Such biphasic changes of T wave form with either right or left sympathetic stimulation have been previously noted and reported, but their signifi cance and mechanisms are unknown [1]

Prolonged nerve stimulation Nerve stimula tion for periods of 30 seconds to 5 minutes was carried out in four experiments In three reduc tion of the QT interval occurred in the other experiment, the QT interval was not altered One

he QT interval in this study Slow infusion of the atecholamines or prolonged sympathetic nerve timulation reduced the duration of the QT inter al. Since all these agencies are known to reduce entricular recovery time the findings suggest hat the observed QT prolongation is the result of localized while QT reduction is the effect of more widespread influence on ventricular recovery * t is well known that the multidirectional atterns of potential differences in the ventricles luring both excitation and recovery cancel many ECG expressions of the processes * In the case of the QT interval the different duration in multiple leads of a normal subject is one evidence that QT duration in a single lead is not an accurate measurement of recovery time If the actual time required for recovery exceeds the duration of the QT interval in the body surface ECG due to cancelling portions of late recovery reduction of recovery time in one of these portions could expose ECG effects of others and prolong the QT interval This mechanism has been previously postulated to explain QT prolon gation due to sympathetic stimulation The study reported here provides new evidence for the mech anism in that the conditions of QT prolongation were ones of localized effects on recovery Rapid catecholamine injection prior to complete intra vascular mixing as well as brief stimulation of nerves with localized cardiac distribution are likely to have localized cardiac effects Slow infusion of catecholamines and prolonged nerve stimulation are likely to have more widespread cardiac effects and were associated with QT interval shortening

The study also furnished evidence that the time required for ventricular recovery exceeds the duration of the QT interval following normal ventricular excitation With ectopic excitation there was a clear increase in QT duration exceeding the increase in QRS interval This suggests that late portions of recovery were not evident in the QT interval following normal excitation and established the conditions neces sary for paradoxical QT prolongation by the postulated mechanism of exposing late recovery effects by accelerated local repolarization

The significance of this study to human electro cardiography is uncertain In certain respects the QT interval duration as a measure of ventricular recovery time is ambiguous In the present study the interval was considered only as an ECG entity descriptive of a particular lead The best ECG measure of ventricular recovery time as a physiologic entity would be provided by multiple leads and by the earliest QTS onset and latest T completion in any lead combination The validity of that assessment of recovery time would however still be subject to the complete ness of the ECG examination and the degree to which cardiac events are expressed in the ECG There are also ambiguities in the measurement of the QT interval which are dependent on T wave form In this study measurements were made visually and a judgment as to the end of the T wave was involved Other measurements such as one based on the most rapid change of slope or the time at which amplitude has reached a particular per cent of peak value can be more precisely de scribed but have no greater validity as measures of physiologic states Finally it is well known that the ECG s of dogs and man differ but it is equally true that detailed studies of body surface potential patterns have substantial similari ties With the known similarities of cardiac electrophysiology and body surface ECG s of dogs and man as well as the limited ECG examinations usually employed for diagnosis it seems likely that phenomena similar to those investigated in this study occur in man In the idiopathic prolonged QT interval syndromes it seems likely that mechanisms other than the specific ones investigated in this study are involved The case reported by Ramon and associates[1] had A V block suggesting actual prolongation of ventric ular recovery rather than simple unmasking of portions of the QT interval Further QT prolon gation in cases of the idiopathic syndromes is frequently of a degree unlikely to be explained by revealing ECG evidence of normal recovery

Although partially speculative the major significance of the study probably concerns vulnerability to cardiac arrhythmias The condi tions in which paradoxical QT prolongation occurred were ones in which the normal disparity of ventricular recovery times was increased Such conditions have been extensively documented to be ones of increased vulnerability to tachycardia and fibrillation Results of this study help explain the associations of QT prolongation and cardiac arrhythmias. They also suggest that paradoxical behavior of the QT interval in relation to changes of ventricular recovery time may be useful as an indicator of cardiac states vulnerable to arrhyth

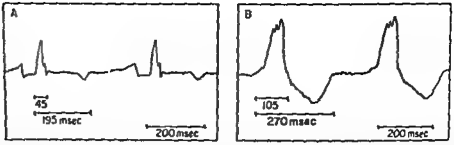

Fig 5 Effect of epicardial ventricular pacing near the pulmonary conus on the QT interval The QRS interval is 60 msec and the QT interval 75 msec longer than those associated with supraventricular activation Other ventricular pacing sites also resulted in greater prolongation of the QT than of the QRS suggesting the abnormal activation orders exposed ECG evidence of ventricular repolarization not apparent in the T wave following normal excitation

anterior ansa stimulation were noted showed 20 msec maximal QT interval reduction

Catecholamine injection Epinephrine, 0 25 mg in 1 c c of solution was rapidly injected intravenously in two experiments and norepinephrine, 0 1 mg in 1 c c of solution was similarly injected in two other experiments The effect of both agents on QT interval was similar consisting of transient QT prolongation followed by QT interval reduction An example of these findings is shown in Fig 4, with QT prolongation at 12 seconds and QT reduction at 2 minutes after injection Increases of QT interval duration amounted to 10 to 20 msec and later decreases in QT duration varied from 10 to 30 msec Three of the eight injections were followed by ventricular tachycardia but QT prolongation occurred preceding the dysrhythmia and while the heart rate was controlled The QT interval reduction in these experiments followed tachycardia but persisted after control of the heart had been reestablished

Slow infusion of 4 mg of norepinephrine in 500 c c of 5 per cent dextrose in water was carried out in two experiments and of 1 mg of epinephrine in 500 c c of water in two other experiments The infusion rate was adjusted to result in alteration of T wave form These interventions resulted in QT interval reduction of 20 to 30 msec and increased amplitude of T waves in the vertical axis ECG lead Increased infusion rate above that required to alter the QT interval resulted in ventricular tachycardia preventing observations of the QT interval pertinent to this study An example of the QT interval reduction produced by epinephrine infusion is shown in the last panel of Fig 4

QT interval duration with ectopic ventricular excitation These observations were made to obtain information pertinent to the mechanism of paradoxical QT interval prolongation That effect seems to require that late portions of ventricular repolarization are not expressed in the normal T wave and can be exposed by reduction of recovery times in part of the cardiac region in which such repolarization occurs This hypothesis permits the prediction that altered activation sequence might sometimes prolong the QT interval by a larger amount than the increase in QRS duration Earlier activation and consequent earlier recovery of part of the region whose normal recovery is late and not expressed in the T wave might expose recovery from other parts of that region This prediction was tested by comparing QT intervals during atrial drive with those during ventricular drive in two experiments An example of findings is illustrated in Fig 5 As shown the supraventricular QRS duration of 45 msec was increased by 60 msec with the heart driven from a site near the pulmonary conus Duration of the QT interval with ventricular drive increased by 75 msec so 15 msec of the QT duration could not be accounted for by increased activation time Other ventricular drive sites all showed QT durations greater than the sum of supraventricular QT duration and the difference of supraventricular and ventricular QRS durations These values ranged from 10 to 50 msec These results provide evidence that late portions of ventricular repolarization are not expressed in the T wave following supraventricular activation and may be exposed to varying degrees by altering recovery sequence secondary to altered excitation order

Discussion

Rapid intravascular injection of epinephrine or norepinephrine or brief stimulation of cardiac sympathetic nerves resulted in prolongation of

The effect of isosorbide dinitrate following experimental coronary occlusion

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Isosorbide dinitrate (ISDN) is described as a long acting nitrate similar to nitroglycerin in its effective relief of angina pain and myocardial ischemia. Clinical studies of ISDN effectiveness have produced contradictory results. Some reports indicate that ISDN administered orally and sublingually is effective in reducing the frequency of angina attacks, reducing left ventricle filling pressure in patients with heart failure, increasing exercise tolerance in patients with angina and reducing ST segment depression during exercise. These reports are contradicted by others in which treatment of angina with similar doses of ISDN did not significantly reduce the frequency of angina pain, nor did it improve exercise tolerance or the exercise electrocardiogram. Measurement of hemodynamic parameters in angina patients indicate an increased heart rate, decreased blood pressure, as well as an increased systemic resistance and decreased cardiac output at rest. Gensini and associates using coronary arteriography reported that ISDN produces coronary artery vasodilation in patients with and without coronary artery disease.

There are too few experimental studies of ISDN action to formulate any generalization concerning its mechanism of action. Studies following experimental coronary occlusion have indicated that ISDN decreases the mortality rate in dogs, but a similar study in baboons showed an increased mortality rate. Evidence for a cardiac effect of ISDN includes a positive inotropic effect of ISDN on isolated papillary muscles and a decreased coronary pressure and resistance after ISDN injection in the coronary artery. The report by Weiss and co workers however indicated that the only significant action of ISDN following coronary occlusion is a decreased systemic blood pressure.

The present experiments are designed to test the effect of ISDN treatment in ameliorating hemodynamic and plasma biochemical changes following experimental coronary artery occlusion in dogs.

Methods

Experimental studies were carried out in male mongrel dogs weighing 20 to 30 kilograms. The animals were anesthetized with sodium pentobarbital (30 mg per kilogram). The coronary occlusion technique was modified from that used by Ribeilima. Catheters were inserted with fluoroscope visualization as follows: (1) femoral vein for measurement of pressures in the right atrium (RA), right ventricle (RV), and pulmonary artery (PA); (2) femoral artery for measuring left atrial (LA) pressures and obtaining arterial blood samples; (3) jugular vein with placement in the coronary sinus for withdrawing venous blood samples and injecting heparin (100 U per kilogram) and maintenance doses of anesthetic; (4) common carotid artery for measuring left ventricle (LV) and aortic (AO) pressures and also withdrawing blood for cardiac output determinations. Coronary occlusion was achieved by placing a catheter in the circumflex branch of the left coronary artery and injecting 1 1 mm diameter stainless steel ball bearings (3 per kilogram). Blood pressures were measured with a

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mıas Agencıes whıch reduce ventrıcular recovery tıme but prolong the QT ınterval and ones whıch prolong recovery tıme but reduce the QT ınterval should be further ınvestıgated as possıble ındıces of cardıac states at hıgh rısk of arrhythmıas

REFERENCES

1 Yanowıtz F Preston J B and Abıldskov J A Functıonal dıstrıbutıon of rıght and left stellate ınnerva tıon to the ventrıcles Productıon of neurogenıc electro cardıographıc changes by unılateral alteratıon of sympa thetıc tone Cırc Res 18 416 1966
2 Moss A J and McDonald J Unılateral cervıcotho racıc sympathetıc ganglıonectomy for the treatment of the long QT ınterval syndrome N Engl J Med 285 903 1971
3 Ramon J H Espınosa A G Reverte F Velasco J Martınez A and Cosın J QT alargado conduccıon AV 2 1 y crısıs sıncopales Presentacıon de un caso revısıon de la lıteratura y consıderacıones fısıopatologıcas Rev Esp Cardıol 25 557 1972
4 Schwartz P J and Mallıanı A Electrıcal alternatıon of the T wave Clınıcal and experımental evıdence of ıts relatıonshıp wıth the sympathetıc nervous system and wıth the long QT syndrome Am Heart J 89 45 1975
5 Han J and Moe G K Non unıform recovery of excıtabılıty ın ventrıcular muscle Cırc Res 14 44 1964
6 Han J Mıllet D Chızzonıttı B and Moe G K Temporal dıspersıon of recovery of excıtabılıty ın atrıum and ventrıcle as a functıon of heart rate Am Heart J 71 481 1966
7 Han J Garcıa de Jalon P D and Moe G K Fıbrıllatıon threshold of premature ventrıcular se quences Cırc Res 18 18 1966
8 Han J Garcıa de Jalon P D and Moe G K Adrenergıc effects on ventrıcular vulnerabılıty Cırc 14 516 1964
9 Moe G K Abıldskov J A and Han J F responsıble for ınıtıatıon and maıntaınence of vent fıbrıllatıon *ın* Surawıcz B and Pellegrıno E D eds ın Sudden Cardıac Death New York 1964 Grune & Stra ton Inc p 56
10 Han J Mechanısms of ventrıcular arrhythmıas asso cıated wıth myocardıal ınfarctıon Am J C 24 800 1969
11 Moe G K and Abıldskov J A Atrıal fıbrıllatıon as self sustaınıng arrhythmıa ındependent of focal dıs charge Am Heart J 58 59 1959
12 Moe G K Rheınboldt W C and Abıldskov J A A computer model of atrıal fıbrıllatıon Am Heart J 67 200 1964
13 Harrıs A S Otero H and Bocage A J The ınductıon of arrhythmıas by sympathetıc actıvıty before and after occlusıon of a coronary artery ın the canıne heart J Electrocardıol 4 34 1971
14 Abıldskov J A and Kleın R M Cancellatıon of electrocardıographıc effects durıng ventrıcular excıta tıon Cırc Res 11 247 1962
15 Schaefer H Uber dıe absolute Grosse elektrokardıogra phıscher Potentıale Pflugers Arch Ges Physıol 255 251 1952
16 Burgess M J Mıllar K and Abıldskov J A Cancel latıon of electrocardıographıc effects durıng ventrıcular recovery J Electrocardıol 2 101 1969
17 Taccardı B Dıstrıbutıon of heart potentıals on dog thoracıc surface Cırc Res 11 862 1962
18 Taccardı B Dıstrıbutıon of heart potentıals on the thoracıc surface of normal human subjects Cırc Res 12 341 1963

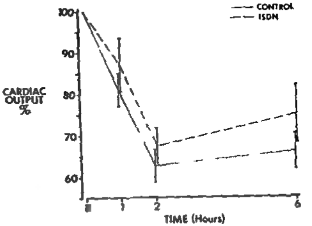
animals The difference in mortality rates is not significant

Effect of ISDN infusion on hemodynamic changes following coronary occlusion The percentages of baseline hemodynamic values at 1 2 and 6 hours following embolization of the circumflex branch of the left coronary artery are shown in Figs 1 and 2 The ISDN treated group is compared with the control group in which embolization was performed but no ISDN administered As Fig 1 indicates following embolization the mean blood pressures decreased more in the ISDN treated animals than in the control animals The ISDN treated animals compared to the control animals had significantly lower absolute mean pressure values in all heart chambers and in systemic and pulmonary circulation at 1 and 2 hours after embolization The blood pressures 6 hours after embolization and ISDN infusion were not significantly different from those without ISDN infusion

Systemic vascular resistance increased following embolization of the left coronary artery in the control animals this increase was significantly less in the ISDN treated animals at 1 hour after embolization but not at 2 or 6 hours (Fig 2) There was no significant difference in pulmonary vascular resistance between the treated and control animals.

Cardiac output changes following embolization are shown in Fig 3 In the ISDN treated animals the decrease in cardiac output was less than in the control group but the differences were not significant Heart rate increased significantly in both groups of animals at 6 hours after embolization Stroke volume decreased significantly following embolization but stroke volume in ISDN treated animals was not significantly different from that in the control animals

Effect of ISDN infusion on plasma biochemical parameters following coronary occlusion The results of the effect of coronary artery embolization and subsequent ISDN infusion on blood biochemical parameters are shown in Table I Coronary sinus values are listed however arterial blood samples were also analyzed and there was no significant difference between the ISDN treated and control animals. The results in Table I show no significant difference in Po_2 and Pco_2. Coronary sinus pH values increased more in the ISDN treated animals than the control group Glucose lactate and pyruvate changed



H.R. (% of base)	C	101	100	121
	I	112	110	138
S.V (% of base)	C	80	63	57
	I	78	62	57

Fig 3 Cardiac output changes following embolization of the circumflex branch of the left coronary artery in a control group of dogs (n = 11) and a group treated with isosorbide dinitrate (ISDN 0 mg intravenous infusion) subsequent to embolization (n = 12) The abscissa represents the time after embolization with *B* representing the pre embolization value The ordinate represents the per cent of pre-embolization value The numbers given beneath the figure represent per cent of baseline values for heart rate (*HR*) and stroke value (*SV*) in control (*C*) and ISDN treated (*I*) animals. There are no significant differences (P > 0 05) between the control and treated groups The vertical bars represent ± S E

significantly following embolization but the values for these parameters in ISDN treated animals were not significantly different from those in the control animals The serum enzymes LDH SGOT and CPK all increased following embolization of the left circumflex artery The only significant difference between the ISDN treated group and the control group is in the CPK 2 and 6 hour samples where the CPK is less in the treated group than in the control group

Discussion

The effectiveness of nitrates in the treatment of angina and ischemic hearts has been explained on the basis of the vasodilation action of nitrates on the coronary arteries [2, 11] An alternate hypothesis is that the nitrates decrease oxygen utilization through vasodilation in the systemic circulation thereby decreasing systemic resistance and cardiac work. The data presented here do not provide evidence for any cardiac effect Cardiac output and stroke volume in the ISDN treated animals following coronary artery occlusion are

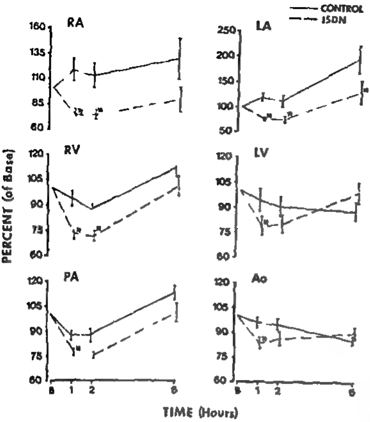


Fig 1 Mean blood pressures following embolization of the left coronary artery in a control group of dogs (n = 11) and a group treated with isosorbide dinitrate (ISDN 20 mg intravenous infusion) following embolization (n = 12) The abscissa represents the time after embolization with B representing the pre embolization value The ordinate is the per cent of baseline value RA = right atrium RV = right ventricle PA = pulmonary artery LA = left atrium LV = left ventricle AO = aorta The vertical lines represent ±S E An asterisk indicates a significant difference ($P < 0.05$) from the corresponding control value

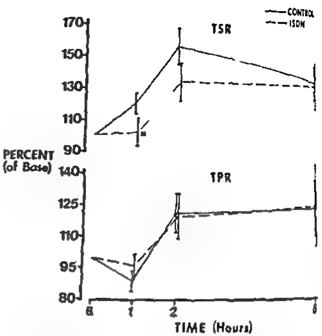


Fig 2 Vascular resistance changes following embolization of the circumflex branch of the left coronary artery in a control group of dogs (n = 11) and a group treated with isosorbide dinitrate (ISDN 20 mg intravenous infusion) subsequent to embolization (n = 12) The abscissa represents time after embolization with B representing the pre embolization value The ordinate = per cent of pre embolization value TSR = total systemic resistance TPR = total pulmonary resistance The vertical lines represent ±S E An asterisk indicates a significant difference ($P < 0.05$) from the corresponding control value

Statham P23D pressure transducer and recorded with a Sanborn Model 150 polygraph recorder Cardiac output was measured by dye dilution with Cardiogreen dye and a Gilford 105 IP densitometer with a Lexington Instruments cardiac output computer Stroke volume was calculated from cardiac output and heart rate Vascular resistance was calculated from arterial atrial pressure difference/cardiac output and expressed as Wood units

Blood samples were withdrawn from the left atrium and coronary sinus for studies of enzymes blood gases, acid base characteristics, and metabolic substrates Analysis procedures were the same as those used previously [1, 22]

The experiments used two groups of animals (1) the myocardial infarct control group of 11 animals in which the left circumflex branch of the coronary artery was occluded by injection of stainless steel ball bearings and (2) the experimental ISDN (Isordil Ives Laboratories) treated animals This group consisted of 12 animals in which ISDN infusion was begun immediately after embolization of the coronary artery, 20 mg of ISDN were administered by a 1 to 2 minute intravenous infusion This dose is equivalent to that used by previous investigators [16, 19]

All hemodynamic parameters were measured and blood samples withdrawn for plasma analysis prior to embolization (base) and were repeated 1 2 and 6 hours after embolization The data from the period after embolization were compared with base values and the data from ISDN treated animals compared with the control group Data were analyzed by group comparison for the calculation of t Differences between values with $P < 0.05$ were considered statistically significant

Results

Mortality rates In the control group three out of 14 animals died following coronary occlusion, two out of 14 died in the ISDN treated group of

decreased tension on the myocardium and consequently a reduced myocardial oxygen consumption The decreased work load also decreases oxygen demand This is consistent with previous reports of decreased systemic pressures following ISDN treatment[19, 4] and the decreased left ventricle filling pressure in patients with heart failure[4] The increased heart rate observed with ISDN treatment is probably a secondary response following the decreased systemic resistance[13, 4]

Although a quantitative estimate of infarct size requires measurement of CPK released from the myocardium[17] the low serum CPK levels at 2 and 6 hours after occlusion in the ISDN treated animals suggest less myocardial damage in the treated animals than in the controls This apparent sparing of the myocardium following coronary occlusion could result from decreased oxygen demand associated with the reduced preload or afterload reported here or from increased oxygen supply associated with coronary vasodilation reported by others[4]

Isosorbide dinitrate is described as a long acting nitrate but the duration of effectiveness has been disputed Aronow[1] and Goldstein et al[3] indicated that ISDN is as effective as the short acting nitroglycerin but only for approximately the same duration of time Other investigators reported responses to ISDN 1 to 2 hours after administration The results presented here indicate a significant difference in systemic and cardiac pressures between the ISDN treated and control animals 2 hours but not 6 hours after ISDN infusion

Summary

The results of the present investigation indicate that ISDN infusion following experimental coronary occlusion in anesthetized dogs (1) lowers systemic cardiac and pulmonary blood pressures (2) decreases systemic resistance (3) has no significant effect on cardiac output heart rate and stroke volume (4) decreases serum CPK levels and (5) has little effect on blood biochemical parameters. These results suggest that ISDN may have a minimal effect on the ischemic heart by means of a slight decrease in peripheral vascular resistance and systemic blood pressure

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REFERENCES

1 Bunn W H and Chremos, A N Clinical evaluation of sublingual nitrates Onset and duration of action of nitroglycerin and isosorbide dinitrate Angiology 14 48 1963
2 Krantz, J [illegible] Action and nomenclature of nitroglycerin and nitrate esters, Am. J Cardiol. 29 436 1972
3 Leslie R. E Nitroglycerin and isosorbide dinitrate in coronary insufficiency Texas Med. 67 95 1971
4 Franciosa, J A. Mikulic E., Cohn J [illegible] Jose N and Fabie A. Hemodynamic effects of orally administered isosorbide dinitrate in patients with congestive heart failure Circulation 50 1020 1974
5 Klaus, A. P Zaret [illegible] L., Pitt B L., and Ross R. S Comparative evaluation of sublingual long acting nitrates, Circulation 48 519 1973
6 Russek, H. I. The therapeutic role of coronary vasodilators Glyceryl trinitrate isosorbide dinitrate and pentaerythritol tetranitrate Am. J Med Sci. 252 9 1966
7 Gorman, P A and Evans, J M The effects of chewable isosorbide dinitrate in coronary insufficiency A report on exercise electrocardiograms in 13 patients, Med. Ann Dist Columbia 40 235 1971
8 Fisch, S and DeGraff A. C Coronary vasodilators, Dis. Chest 44 533 1963
9 Goldbarg. A. N., Moran J F Butterfield T K Nemickas, R and Bermudez, G A. Therapy of angina pectoris with propranolol and long acting nitrates Circulation 40 847 1969
10 Aronow W S and Chesluk, H. M Sublingual isosorbide dinitrate therapy versus sublingual placebo in angina pectoris, Circulation 41 869 1970
11 Livesley B Catley P F Campbell, R C and Oram S Double-blind evaluation of verpamil, propranolol and isosorbide dinitrate against a placebo in the treatment of angina pectoris, Br Med. J 1 375 1973
12 Russek, H I Propranolol and isosorbide dinitrate synergism in angina pectoris, Am J Cardiol. 21 44 1968
13 Sweatman, T Strauss G Selzer A and Cohn K E The long acting hemodynamic effects of isosorbide dinitrate Am. J Cardiol. [illegible] 475 1972
[illegible] Gensini G G Kelly A E., DeCosta B C B., and Huntington, P P Quantitative angiography The measurement of coronary vasomobility in the intact animal and man, Chest 60 522 1971
15 Hedges, R. N and Somerndike J M Nitrate therapy in experimental coronary occlusion Presbyterian St. Luke's Med Bull. 2 31 1963
16 Seljeskog, E. L., Hitchcock, C R., Groover M F., Haglin J J and Strobel, C J A Isosorbide dinitrate during acute coronary occlusion Effects in the baboon J A. M A. 183 210 1963
17 Strauer B E. Isosorbide dinitrate Its action on myocardial contractility in comparison with nitroglycerin, Int. J Clin Pharmacol. 8 30 1973
[illegible] Case R. B., Raven R. B and Crampton R S Benign coronary dilating action of nitroglycerin and isosorbide dinitrate, Circulation 30 (Suppl. III) [illegible] 1964
19 Weiss, A. B Senft, A., Khan M I and Regan, T J Effect of nitrate infusions on the systemic and coronary circulations following acute myocardial infarction in the intact dog, Am. J Cardiol. 30 362, 19 2
20 Rübeuma, J Selective embolization of the coronary arteries—a hemodynamic, metabolic and radiologic study Proc. Soc. Exp Biol Med. 117 367 1964

Table 1 Comparison of blood biochemical parameters in ISDN treated and control dogs following experimental coronary artery occlusion

	Time following coronary artery occlusion			
	Base $\bar{X} \pm SE$	1 Hr $\bar{X} \pm SE$	2 Hr $\bar{X} \pm SE$	6 Hr $\bar{X} \pm SE$
CS Po_2 (mm Hg)				
C (10)	29 0 ± 1 3	25 3 ± 2 2	24 7† ± 1 8	24 6† ± 1 4
ISDN (12)‡	28 9 ± 2 8	23 9 ± 2 7	23 2 ± 2 5	23 8 ± 3 [illegible]
CS Pco (mm Hg)				
C (10)	49 5 ± 4 1	41 8 ± 4 8	36 6† ± 2 6	43 6 ± 3 9
ISDN (12)	6[illegible] 8* ± 3 4	46 6† ± 3 2	44 2† ± 3 7	36 8† ± 3 1
CS pH				
C (10)	[illegible]36 ± 0 02	7 37 ± 0 02	7 38 ± 0 02	7 34 ± 0 0[illegible]
ISDN (12)	7 29 ± 0 01	7 34† ± 0 02	7 35† ± 0 02	7 41†* ± 0 03
CS glucose (mg /100 ml)				
C (11)	110 0 ± 4 9	99 3 ± 4 1	69 8† ± 5 7	83 2† ± 4 2
ISDN (11)	99 9 ± 6 2	100 6 ± 4 6	93 3 ± 6 5	84 2† ± 6 1
CS lactate (mg /100 ml)				
C (10)	7 0[illegible] ± 1 16	13 03† ± 1 74	12 66† ± 2 17	11 98† ± 2 61
ISDN (12)	[illegible]20 ± 0 82	10 98† ± 1 92	10 82† ± 1 55	8 56† ± 1 [illegible]
CS pyruvate (mg /100 ml)				
C (10)	0 567 ± 0 043	0 817† ± 0 040	0 820† ± 0 0[illegible]2	0 922† ± 0 093
ISDN (12)	0 463 ± 0 054	0 768† ± 0 119	0 761† ± 0 136	0 792† ± 0 1[illegible]9
CS FFA (mEq /l)				
C (11)	499 0 ± 43 0	381 0† ± 32 0	475 0 ± 66 0	724 0† ± 109 0
ISDN (12)	343 0 ± 24 0	313 0 ± 28 0	344 0* ± 38 0	673 0† ± 162 0
CS LDH (I U /ml)				
C (11)	40 1 ± 6 8	77 9† ± 10 4	161 1† ± 42 3	358 0† ± 50 4
ISDN (12)	72 2 ± 8 4	134 5† ± 11 4	294 7† ± 77 7	510 1† ± 10[illegible] 3
CS SGOT (I U /ml)				
C (11)	28 5 ± 4 4	54 9† ± 10 1	128 5† ± 33 6	343 4† ± 1[illegible]6 [illegible]
ISDN (12)	19 4 ± 3 9	35 9 ± 9 2	[illegible]3 3† ± 24 0	347 3 ± 1[illegible]0 3
CS CPK (I U /ml)				
C (11)	5 3 ± 0 4	12 5† ± 3 9	58 2 ± 15 8	235 8† ± 164 3
ISDN (12)	8 3 ± 1 4	11 7 ± 1 8	24 8† ± 3 7	98 0†* ± 1[illegible]2

Indicates significant difference ($P < 0.05$) from corresponding control value
†Indicates significant difference ($P < 0.05$) from corresponding base value
‡ISDN = Isosorbide dinitrate (20 mg intravenous infusion) FFA = plasma free fatty acid concentration LDH = serum lactic dehydrogenase activity SGOT = serum glutamic oxaloacetic transaminase activity CPK = serum creatine phosphokinase activity

not significantly different from those in the control animals Blood Po_2 Pco, lactate, pyruvate, glucose, LDH, and SGOT in the ISDN treated animals are not significantly different from those in the controls This evidence suggests no significant effect of ISDN on myocardial contractility or metabolism This is consistent with the data of Weiss and co workers [18] which show no significant effect of ISDN on cardiac index or coronary blood flow following coronary occlusion Conflicting evidence includes the positive inotropic effect of ISDN on isolated papillary muscles[11] and coronary artery vasodilation in response to ISDN observed through coronary arteriography [14]

Evidence supporting the hypothesis that ISDN is effective because of its action on the peripheral vasculature includes the decreased systemic cardiac and pulmonary pressures reported here The vasodilation indicated by the decreased systemic resistance and pressures decreases the afterload on the heart and the decreased atrial pressures indicate a decreased preload This decrease in afterload and preload indicates a

Differing mechanisms for ventricular vulnerability during coronary artery occlusion and release

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Although these models may have direct relevance to the occurrence of sudden death in man there is a paucity of information on VF threshold changes in these two phases and the mechanisms have not been adequately defined The present study had three objectives (1) to analyze the time course of enhanced susceptibility to VF during coronary artery occlusion and release (2) *to determine the duration of coronary occlusion* required for the provocation of VF on release and (3) to compare the effects of various drugs on cardiac vulnerability during coronary artery release as well as occlusion

Material and methods

Operative procedure Forty eight mongrel dogs of either sex, weighing 16 to 25 kilograms were utilized in the present study One week prior to definitive investigation the dogs were anesthetized with sodium pentobarbital (30 mg per kilogram) and artificial ventilation was instituted. With sterile technique a left thoracotomy was performed through the fourth intercostal space The heart was exposed and a balloon occluder (Brunswick Corp) was placed around

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Differing mechanisms for ventricular vulnerability during coronary artery occlusion and release

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Clinical and experimental observations indicate that catastrophic arrhythmias occur during the very inception of myocardial infarction Among patients electrical failure has its highest prevalence within the first hour after onset of an ischemic event[1] The mechanism for death is almost invariably ventricular fibrillation (VF) It has been assumed that impaired coronary arterial flow is the basis for the VF resulting from electrical derangements in the myocardium consequent to hypoxia and ischemia In experimental animals however VF follows not only during obstruction but also upon the re establishment of coronary flow In fact it has been reported that as compared to coronary artery occlusion release of the obstruction is nearly twice as effective in provoking VF[2]

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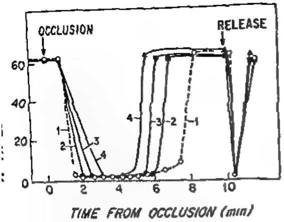

Fig. 1 Time course of the ventricular fibrillation (VF) threshold changes during and upon release of repeated 10 minute occlusions of the left anterior descending coronary artery in 10 dogs. During the first occlusion (open circles) VF threshold decreased from a mean of 63 mA to 2 mA. This occurred within 1 minute of occlusion and persisted for 6 minutes. *Upon release of occlusion VF threshold again fell to* 4 mA. This decrease was rapid in onset and persisted only transiently. With subsequent occlusions, a reduction in fibrillation threshold still occurred but the time of onset of the effect was delayed and the total period of enhanced vulnerability was diminished. The VF threshold changes following release were unaltered by repeated periods of myocardial ischemia.

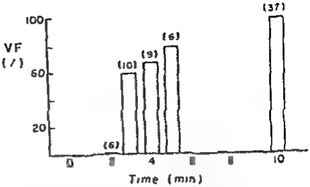

Fig. 2 Incidence of VF (provoked by low-current [2 mA] R/T pulses) during coronary artery release as a function of duration of occlusion in seven dogs. When the period of myocardial ischemia was less than 3 minutes, VF was not provoked upon release of occlusion. With longer periods of ischemia the incidence of release-induced VF increased from 60 per cent with 3 minutes of occlusion to 97 per cent with 10 minutes of occlusion. The numbers in parentheses refer to the number of occlusion trials. Data for the 10 minute occlusion were obtained from 11 additional dogs.

of isoproterenol. Determinations of refractory periods and VF threshold were made prior to and 20 minutes following propranolol infusion. The effect of propranolol on VF threshold changes associated with 10 minutes of coronary artery occlusion and release was studied at 30, 60, 120 and 180 minutes after administration of the drug.

Phentolamine. Alpha adrenergic blockade was induced in eight dogs by an intravenous infusion of 0.1 mg per kilogram of phentolamine over a 10 minute period. Measurements of refractory periods and VF threshold were made before and during coronary artery occlusion as described above for propranolol.

Lidocaine. The effect of lidocaine treatment was studied in 11 dogs. The drug was administered in a constant infusion (70 µg per kilogram per minute) following a loading injection (2 mg per kilogram). Plasma levels of lidocaine ranging from 3.5 to 6.1 µg per milliliter were achieved within 3 minutes after the start of infusion and were maintained within this range throughout the course of an experiment. These were analyzed

Table 1 Effect of various drugs on VF threshold (milliamperes) prior to coronary artery occlusion (means ± S.E.)

	Control	30 minutes after drug injection	P value
Propranolol (n = 11)	54 ± 5	89 ± 4	< 0.001
Phentolamine (n = 8)	55 ± 10	56 ± 10	N.S.
Lidocaine (n = 11)	[illegible] ± 2	60 ± 4	N.S.

Value determined 5 minutes after commencing continuous infusion of this drug.

according to the method of Sung and Truant.[11] Electrical testing of the heart was performed prior to and 5 minutes after onset of drug infusion. The VF threshold change associated with coronary artery occlusion and release was studied at 30, 60, 120 and 180 minutes after institution of lidocaine infusion.

Results

VF threshold during coronary artery occlusion and release. The time course of change in VF threshold following a 10 minute period of LAD coronary artery occlusion was studied in 11 dogs. A decrease in threshold from 63 ± 3 mA (S.E.) to

the left anterior descending (LAD) coronary artery, 1 cm from its origin and just distal to the first diagonal branch Care was taken not to compromise patency of the vessel The inflation tubing of the balloon occluder was exteriorized at the nape of the neck via a subcutaneous tunnel and the thoracotomy incision was closed Electro cardiograms (ECG) were continuously monitored thereafter for 24 hours with an automated direct printout Dogs exhibiting ventricular arrhyth mias during the postoperative period were elimi nated from the study

Experimental procedures On the day of inves tigation the dogs were anesthetized with sodium pentobarbital (30 mg per kilogram) and artificial ventilation was established by means of a Bird Mark 14 respirator supplied with 100 per cent oxygen Arterial pH was maintained in the range of 7 35 to 7 50 and Po_2 greater than 100 mm Hg Rectal temperature was also monitored and maintained at 37 ± 1° C with a thermal blanket A tripolar cardiac catheter (USCI 7F platinum pole with interelectrode distance of 1 cm and pole width of 2 mm) was positioned under fluoroscop ic control in the apex of the right ventricle via a jugular vein The proximal pole was utilized to obtain an intracavitary ECG, whereas the remaining two poles were employed for ventric ular pacing and pulsing Systemic blood pressure was recorded from a cannula placed in a femoral artery Drugs were infused through a femoral vein

VF threshold was determined according to the sequential R/T pulsing technique described previously[8, 11] Sequences of three pulses are deliv ered 10 msec beyond the boundary of the effec tive refractory period (determined by a stimulus of twice threshold intensity) of each preceding beat To determine the fibrillation threshold, the current of the third pulse is increased in 5 mA increments until VF supervenes The current which consistently evokes VF defines the VF threshold

The specific testing procedure employed in the present study is as follows Two determinations of VF threshold were made just prior to coronary artery occlusion Values usually agreed within 5 mA The LAD coronary artery was then com pletely occluded for 10 minutes by inflating the previously implanted balloon catheter During coronary artery occlusion the VF threshold was assessed at 1 minute intervals until recovery of preocclusion values were re established Th usually occurred within 4 to 8 minutes afte balloon inflation At 10 minutes the ba catheter was abruptly deflated The changes in fibrillation threshold in response to release of occlusion were rapid in onset and brief in dura tion R/T testing was therefore commenced immediately upon release with the current of S fixed at twice the mid diastolic value for a propa gated response (2 to 5 mA) When VF could no longer be induced, the intensity of the pulse was increased as described above Complete recovery of the fibrillation threshold usually was observed within less than 3 minutes following release of occlusion Whenever VF occurred unprovoked by pulsing, as it did on occasion during coronary artery occlusion and release the rhythm was abruptly terminated by countershock and the testing procedure was resumed Defibrill could be accomplished usually within 3 to seconds by a DC pulse (50 to 150 Wsec capaci discharge from a Lown Cardioverter) deliver through copper paddles (100 cm^2) which had previously applied across the chest The effect of repeated fibrillation and defibrillation on the VF threshold was tested in the unoccluded state in six dogs and was found to be without significant effect on the stability of the VF threshold (i e the fibrillatory current did not vary by more than 5 mA) A rest period of 20 minutes was allowed after each coronary occlusion trial During VF threshold testing the heart was paced at a constant rate of 200 b p m

The effect of varying the duration of occlusion on the occurrence of vulnerability during release was studied in seven dogs In these dogs the period of occlusion ranged from 2 to [illegible] minutes The length of the occlusion was randomized and a rest period of 20 minutes was allowed between experi mental trials In this series of experiments sequential R/T pulsing was performed only upon release of occlusion with S_3 set at twice the mid diastolic value

Pharmacologic interventions

Propranolol Beta adrenergic blockade was induced in 11 dogs by intravenous infusion of 0 2 mg per kilogram of propranolol (Inderal) over a 10 minute period This dose was sufficient to prevent 80 per cent of the chronotropic response to a 1 0 μg per kilogram injection (over 2 minutes)

ıll ın threshold following coronary occlusion 'his antifibrillatory effect gradually subsided 'ver the 2 hour period of study Propranolol owever did not affect the VF threshold change ollowing release of coronary artery occlusion Fig. 3)

Phentolamine Alpha adrenergic blockade was nduced in eight dogs by injection of phentolam ne Although this drug did not significantly alter VF threshold prior to occlusion (Table I) it was nevertheless effective in reducing the vulnerability changes associated with myocardial ischemia. Phentolamine did not however prevent the reduction in VF threshold attending release of occlusion (Fig 4)

Lidocaine The effect of lidocaine administration of the VF threshold during coronary artery occlusion and release was studied in 11 dogs Lidocaine did not alter VF threshold prior to occlusion and was without effect on the threshold changes associated with either coronary occlusion or its release (Table I Fig 5)

Discussion

The present study extends the findings of Axelrod and associates who followed the time course of ventricular vulnerability during coronary occlusion and release in the dog Utilizing the technique of sequential R/T pulsing these workers noted that within 3 minutes after balloon inflation the fibrillation current decreased from 56 ± 7 (mean ± S E) to 1 6 ± 0 3 mA and the vulnerable period duration lengthened These changes lasted only about 4 minutes On reperfusion there was a prompt and transient relowering of the VF threshold The changes in cardiac vulnerability described by both Axelrod and associates and the present investigators coincide with the time course of emergence and recession of ventricular arrhythmias following acute coronary artery occlusion and its release

The arrhythmias occurring on occlusion and release differ An arrhythmia free interval of 1 to 3 minutes ■ observed after occlusion Ectopic activity begins sporadically after increasing in frequency and multiformity these salvos culminate after a variable interval of 1 or more minutes, in VF The occurrence of ectopic activity parallels the development of ECG changes of myocardial injury and ischemia with rising ST segment peaking of T waves and waxing in T wave amplitude The arrhythmic period has a duration of about ■ minutes and coincides temporally with the interval of marked reduction in VF threshold By contrast after reperfusion VF emerges abruptly within seconds while ECG evidence of ischemia is rapidly waning Harbinger ectopic activity is absent The only prodrome to VF is ventricular tachycardia of the vulnerable period[13] The vulnerable period threshold drops sharply to return almost immediately to control levels

The present study points to more specific differences between occlusion and release which shed some light on underlying mechanisms When occlusion release sequences are repeated the onset of enhanced vulnerability for VF is delayed and its duration is abbreviated No such effects are noted on VF threshold following reperfusion Of greater importance is the fact that the changes in cardiac vulnerability following occlusion are nearly annulled by beta and alpha adrenergic blocking drugs however the VF threshold following release is completely unaffected

The present study provides additional evidence that adrenergic influences are critical in the genesis of ventricular arrhythmias following acute coronary occlusion Gillis has found that coronary occlusion in the cat is associated with an increase in electrical activity in parasympathetic and sympathetic fibers and that ablation of these fibers prolonged survival and reduced the incidence of VF It ■ unlikely that enhanced vagus nerve discharge is responsible for the observed fall in VF threshold In fact vagus stimulation raises rather than lowers fibrillation threshold[4] by opposing the effects of neural[4] and humoral[17] activation of the sympathetic nervous system activation

Immediately upon onset of acute myocardial infarction there is a surge of sympathetic discharge[8] Malliani and associates[18] recorded increased firing rate from preganglionic sympathetic fibers at the T_3 level in cats which had sustained occlusion of the left coronary or one of its arterial branches Over 40 years ago Leriche and co workers demonstrated a salutory effect of cardiac sympathectomy in animals with coronary occlusion Our finding that propranolol prevented the fall in fibrillation threshold following coronary artery occlusion indicates that excitation of beta adrenergic receptors by the sympathetic nervous system is largely responsible for the observed increase in susceptibility to VF

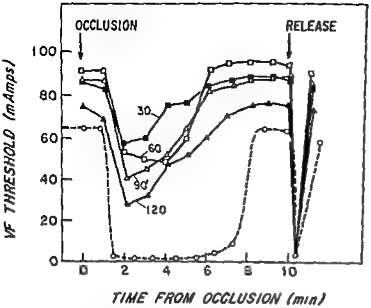

Fig 3 Effect of propranolol induced beta adrenergic blockade on the VF threshold changes associated with coronary artery occlusions and release in 11 dogs The number beside each curve refers to the time following drug administration The dashed line depicts the pattern of threshold changes observed during the initial occlusion in untreated dogs (see Fig 1) Propranolol administration increased the VF threshold by 64 per cent with the coronary circulation intact and significantly diminished the decrease in fibrillation threshold during coronary occlusion This drug however was without effect on the threshold changes associated with release of occlusion

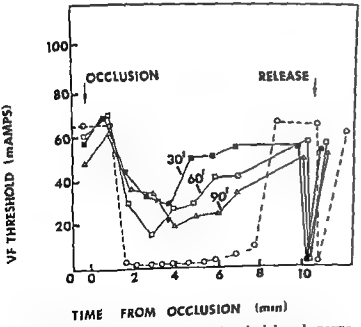

Fig 4 Influence of phentolamine-induced alpha adrenergic blockade on the VF threshold changes during coronary artery occlusion and release in eight dogs Phentolamine did not alter VF threshold in the unoccluded condition Nevertheless this drug did afford significant protection against the fall in fibrillation threshold during coronary occlusion As with propranolol this agent was without effect on the release phenomenon

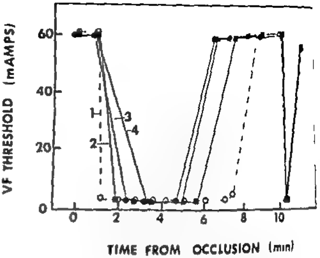

Fig 5 Influence of lidocaine administration on the VF threshold alterations associated with coronary artery occlusion and release in 11 dogs Lidocaine was completely without effect on the fibrillation threshold either prior to or during coronary artery occlusion and release

2 mA (mid diastolic threshold) was noted within 1 2 ± 0 1 minutes following occlusion and was strikingly precipitous This reduction persisted for 6 0 ± 0 5 minutes Thereafter there was an abrupt return to the preocclusion threshold. Upon release of occlusion the fall in fibrillation threshold was nearly immediate occurring within 0 2 ± 0 02 minute of release and was transient in duration With repeated occlusion, the onset in VF threshold lowering was progressively delayed and the total period of enhanced vulnerability was significantly decreased No such changes were observed following repeated releases of occlusion (Fig 1)

The relation between duration of occlusion and vulnerability for VF during release was studied in seven dogs When the period of ischemia was less than 3 minutes VF could not be induced following release by low current pulses of 2 mA As the period of occlusion was extended, the incidence of VF following release increased in response to sequential R/T pulsing Thus with a duration of occlusion of three minutes a 60 per cent incidence of VF was noted as compared to 97 per cent when occlusion was maintained for 10 minutes (Fig 2)

Pharmacologic interventions

Propranolol The effect of propranolol induced beta adrenergic blockade on the VF threshold during coronary artery occlusion and release was studied in 11 dogs Propranolol administration substantially increased VF threshold prior to occlusion (Table I) and greatly diminished the

le in the increased susceptibility to VF asso ated with acute myocardial ischemia whereas e changes in VF threshold following reperfusion ay be due to washout products of cellular chemia These findings support the view that otection against VF during coronary artery clusion and release may require different ntiarrhythmic measures

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RENCES

Wikland, B Medically unattended fatal cases of ischemic heart disease in a defined population Acta Med Scand. (Suppl) 524 1971
Fulton M Julian D G and Oliver M F Sudden death and myocardial infarction Circulation 40 (Suppl. IV) IV 182 1969
Lown B and Wolf M Approaches to sudden death from coronary heart disease Circulation 44 130 1971
Lown B Sudden death from coronary heart disease *in* Waldenstrom J Larsson T and Ljungstedt N Editors Early phases of coronary heart disease The possibility of prediction (Skandia International Symposia) Stockholm 1973 Nordiska Bokhandelns Forlag pp 255 277
Adgey A. A. J Allen J D Geddes, J S James R G W Webb S W Zaidi, S A and Pantridge J F Acute phase of myocardial infarction Lancet 2 501 1971
Stephenson S E Cole R K Parrish, T F Bauer F M Johnson J T Jr Kochtitzky M Anderson J S Jr Hibbitt L. L. McCarty J E Young, E R Wilson J R., Meiers, H N Meador C K Ball C O T and Meneely G R Ventricular fibrillation during and after coronary artery occlusion Incidence and protection afforded by various drugs, Am. J Cardiol. 5 77 1960
Harris A S Delayed development of ventricular ectopic rhythms following experimental coronary occlusion *Circulation 1 1318 1950*
Harris, A. S Factors which determine prognosis in experimental coronary occlusion *in* Surawicz B and Pellegrino E D Editors Sudden cardiac death, New York, 1964 Grune & Stratton Inc p 110
Thompson P and Lown B Sequential R/T pacing to expose electrical instability in the ischemic ventricle Clin Res. (abst) 20 401 1972
Axelrod, P J Verrier R L and Lown B Vulnerability to ventricular fibrillation (VF) during acute coronary occlusion and release Am J Cardiol. 36 6 1975
Verrier R Calvert A Lown B and Axelrod, P Effect of acute blood pressure elevation on the ventricular fibrillation threshold. Am J Physiol. 226 893 1974
2. Sung, C Y and Truant, A. P The physiologic disposition of lidocaine and its comparison in some respects with procaine J Pharmacol Exp Ther 112 432 1954
3. Wolff G A Vieth F and Lown B A vulnerable period for ventricular tachycardia following myocardial infarction Cardiovasc Res. 2 111 1968
4. Gillis, R A Role of the nervous system in the arrhythmias produced by coronary occlusion in the cat, AM HEART J 81 677 1971
5. Kent, K M Smith E R Redwood, D R and Epstein S. R. Electrical stability of acutely ischemic myocardium Influences of heart rate and vagal stimulation Circulation 47 291 1973
16 Kolman, B., Verrier R L. and Lown B The effect of vagus nerve stimulation upon vulnerability of the canine ventricle Role of sympathetic parasympathetic interactions, Circulation 52 5 8 1975
17 Verrier R. L., Rabinowitz, S H., and Lown B Vagal and adrenergic interactions and ventricular electrical stability Clin. Res. (abst.) 23 212A 1975
18. Brown A. M Excitation of afferent cardiac sympathetic nerve fibers during myocardial ischemia J Physiol (Lond) 190 35 1967
19 Malliani, A Schwartz, P J and Zanchetti, A A sympathetic reflex elicited by experimental coronary occlusion Am. J Physiol. 217 703 1969
20 Leriche R Herrmann L and Fontaine R. Ligature de la coronaire gauche et fonction cardiaque chez l animal intact C R Soc Biol (Paris) 107 545 1931
21 Han, J Garcia de Jalon P., and Moe G K Adrenergic effects on ventricular vulnerability Circ Res. 14 516 1964
22. Verrier R. L. Thompson P., and Lown B Ventricular vulnerability during sympathetic stimulation Role of heart rate and blood pressure Cardiovasc Res. 8 602, 1974
23. Kliks, B R Burgess, M J and Abildskov J A. The influence of sympathetic tone on ventricular fibrillation threshold during experimental coronary occlusion, Circulation 46 (Suppl. II) II 115 1972.
24 Ebert, P A Vanderbeek R B Allgood R J., and Sabiston, D C Effect of chronic cardiac denervation on arrhythmias after coronary artery ligation Cardiovasc Res. 4 141 1970
25 Harris, A. S Estandia, A., and Tillotson R F Ventricular ectopic rhythms and ventricular fibrillation following cardiac sympathectomy and coronary occlusion Am J Physiol. 165 505 1951
26 Lucchesi, B R Whitsitt, L S and Stickney J L Antiarrhythmic effects of beta adrenergic blocking agents, Ann N Y Acad. Sci. 139 940 1967
27 Harris, A. S and Abdo B Effects of sympathetic blockade on ventricular tachycardia resulting from myocardial infarction Am. J Physiol. 181 559 1955
28 Khan M. I Hamilton J T and Manning, G W Protective effect of beta adrenoceptor blockade in experimental coronary occlusion in conscious dogs, Am. J Cardiol. 30 832 1972
29 Fitzgerald, J D Perspectives in adrenergic beta receptor blockade Clin Pharmacol Ther 10 292 1969
30 Grayson, J Irvine M., Parrat, J R and Cunningham J Vasospastic elements in myocardial infarction following coronary occlusion in the dog Cardiovasc Res. 2 54 1968
31 Grayson J and Lapin B A. Observations on the mechanisms of infarction in the dog after experimental occlusion of the coronary artery Lancet 1 1288 1966
32. Manning, G W McEachern C G and Hall, G E Reflex coronary artery spasm following sudden occlusion of other coronary branches, Arch. Intern Med 64 661 1939
33 Surawicz, B Ventricular fibrillation Am J Cardiol 28 268, 1971
34 Petropoulos, P C., and Jayne N G Cardiac function during perfusion of the circumflex coronary artery with venous blood, low molecular weight dextran or Tyrode solution, AM HEART J 68 370 1964
35 Sewell, W M Koth, D R and Huggins, C E Ventric

There is ample evidence already reported to permit such an inference Direct stimulation of cardiac sympathetic nerves profoundly increases ventricular vulnerability[21,3], furthermore sympathectomy by surgical[4,5] and pharmacologic[6,8] means reduces the incidence or completely prevents the occurrence of VF following coronary artery occlusion It is unlikely that in the present experiment the effect of propranolol was through its quinidine like antiarrhythmic action since the dose employed was well below that required for membrane stabilization[29]

The fact that phentolamine also afforded protection against the reduction in fibrillation threshold following coronary occlusion suggests that alpha as well as beta stimulating sympathetic activation is involved An antifibrillatory action of phentolamine after coronary occlusion has been documented by other workers[6,27] It remains unclear, however, whether phentolamine exerts its antiarrhythmic influence through a direct action on myocardial alpha receptors or by an indirect effect of blocking coronary artery vasospasm which has been postulated to occur during myocardial ischemia[30,32] The fact that the alpha stimulator phenylephrine, is without effect on fibrillation threshold when its pressor response is controlled[11] is consistent with the hypothesis that phentolamine influences VF threshold through an effect on coronary vascular tone

The present investigation suggests that an entirely different mechanism accounted for the lowered VF threshold on release of coronary artery obstruction There is evidence that washout products of ischemic cells are implicated[33] It has been found that if blood flow is gradually returned to the ischemic myocardium[34,35] or if perfusion is maintained with unoxygenated fluid upon re establishing coronary blood flow the prevalence of arrhythmia is reduced[34,36,37] The fact that VF emerges within a few seconds after restoration of flow argues for washout products Our observation that several minutes of ischemia were required to elicit enhanced vulnerability during reperfusion provides additional support for this hypothesis Although blood constituents responsible for the increased vulnerability have not been identified Harris and co workers[9,38,39] have provided data suggesting that potassium might be involved They have demonstrated that intracoronary injection of small amounts of potassium ca[n] precipitate major arrhythmias[3] The concentra[tion] of this ion in the coronary veins drain[ing] ischemic tissue increases rapidly after coron[ary] ligation, reaching peak levels within 8 to 1[?] minutes[15] Our finding that susceptibility to VF during reperfusion was maximal after 10 minutes of occlusion is consistent with the concept that washout of potassium accumulated during the ischemic phase may be responsible for the release phenomenon

It is concluded that enhanced activity of the sympathetic nervous system plays a key role in the increased susceptibility to VF associated with acute myocardial ischemia The changes in vulnerability to VF during reperfusion may be due to washout products of cellular ischemia It may be that the abrupt onset of VF without prodromal ectopic activity seen clinically represent instances of release of coronary spasm which induced sufficient ischemia to cause washout of cell constituents If this is indeed true, different antiarrythmic measures will be required to combat the VF which is associated with impaired flow from that resulting from restored flow

Summary

The time course and mechanism of vulnera[-]bility to ventricular fibrillation (VF) during a 1[0] minute occlusion of the left anterior descendin[g] coronary artery and following its release wer[e] studied in 48 dogs VF threshold was determine[d] by inducing a sequence of three extrasystol[es] (sequential R/T pulsing) Within 1 minute [of] occlusion the fibrillation current decreased to th[e] level required for eliciting a propagated diastoli[c] response This state of enhanced vulnerabilit[y] lasted for approximately [?] minutes, after whic[h] the VF threshold returned to preocclusion value The vulnerability changes upon reperfusion b[y] comparison occurred within seconds of releas[e] and persisted only transiently Three minutes [of] occlusion was the minimal time which resulted i[n] a reduction in VF threshold after release Alpha and beta adrenergic blockade with phentolamin[e] and propranolol respectively prevented th[e] decrease in VF threshold during occlusion bu[t] were without effect upon threshold change[s] during coronary artery release Lidocaine failed to alter the pattern of vulnerability It is concluded that adrenergic mechanisms play a key

ular fibrillation in dogs after sudden return of flow to the coronary artery, Surgery 38 1050 1955
36 Bagdonas A A, Stuckey, J H and Piera, J Effects of ischemia and hypoxia on the specialized conducting system of the canine heart AM HEART J 61 206 1961
37 Danese C Pathogenesis of ventricular fibrillation in coronary occlusion J A M A 179 52 1962
38 Harris A. S Bisteni, A Russel R A P and Firestone, J Excitability factors in tachycardia resulting from myocardial ischemia sium a major excitant Science 119 200 1954
39 Harris A. S Potassium and experimental occlusion AM HEART J 71 797 1966

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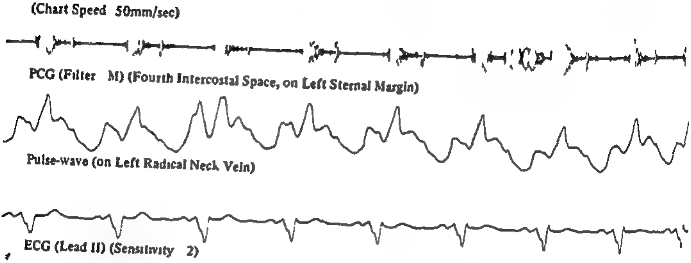
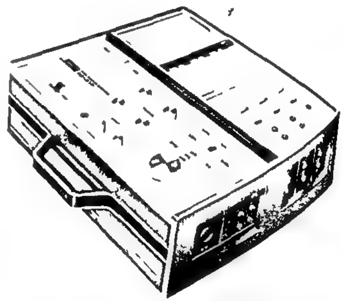


▪ Example 30 year-old male WPW Syndrome (Ebstein's sign)



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directional tachycardia with normal QRS duration

win L Rothfeld M D
ark N J

directional tachycardia (BT) is an uncommon rhythmia that usually occurs in patients who ive advanced heart disease digitalis toxicity id ■ poor prognosis Although originally de ribed in 1922 by Schwensen its origin and iechanism are still not entirely clear and ontroversy exists as to whether BT is a supra entricular tachycardia with alternating aber ant intraventricular conduction or an ectopic entricular rhythm While approximately 75 ases have been described there is only one ublished example of BT with QRS complexes of iormal duration throughout the tachycardia[2] I iave recently seen another instance of BT with thin QRS complexes in a 76 year old woman with terminal rheumatic heart disease and digitalis toxicity and I feel that this rare occurrence merits publication

Case report

A 6-year old woman with long standing rheumatic mitral stenosis and insufficiency and chronic atrial fibrillation was rehospitalized on Jan 26 19 5 because of increasing dyspnea orthopnea and left lateral pleuritic chest pain Her daily medications included digoxin (0 5 mg) and furosemide (80 mg.) *Physical examination showed a tachypneic cyanotic* woman who appeared both acutely and chronically ill There was atrial fibrillation with a rapid entricular rate murmurs of mitral stenosis and insufficiency bibasilar fine rales, and a loud pleural rub over the left lateral chest The admission electrocardiogram (ECG) disclosed coarse atrial fibrillation with a rapid ventricular rate biventricular hypertrophy and digitalis repolarization effects (Fig 1) A chest x ray revealed pancardiac dilatation with pulmonary venous and arterial hypertension Initial laboratory abnormalities included mild hypokalemia (3 3 mEq per liter) and azotemia (48 mg per deciliter)

Furosemide (60 mg) was given intravenously and 0 5 mg of digoxin was administered orally in divided doses About 12 hours later there was a significant decrease in entricular rate and brief runs of BT with QRS complexes of normal duration occurred (Fig. 2 *A*) Serum immunoassay for digoxin was 3.1 ng per deciliter at this time The BT became the dominant rhythm on the second hospital day and proved resistant to intravenous potassium diphenylhydantoin lido-caine procaineamide and propranolol (Fig 2 *B* and *C*) The patient died in pulmonary edema approximately 2 hours after admission. Autopsy showed generalized visceral congestion multiple pulmonary infarcts pulmonary edema marked cardiomegaly and severe rheumatic mitral stenosis and insufficiency with extensive myocardial fibrosis

Discussion

Cohen and associates after reviewing 72 cases of BT concluded that it occurred in patients with advanced heart disease chronic atrial fibrillation evidence of digitalis toxicity and an extremely poor prognosis most were dead within hours to days *after the onset of the arrhythmia Interest* ingly the ECG s usually showed right bundle branch block in chest leads and alternating left anterior and left posterior hemiblock in limb leads This remarkably constant pattern led Rosenbaum and associates to hypothesize that BT was a supraventricular tachycardia with permanent aberrant conduction in the right bundle branch and alternating aberrant conduc tion in the two fascicles of the left bundle branch Other supportive evidence for a supraventricular origin includes the common association of BT with supraventricular arrhythmias like junc tional tachycardia and the fact that episodes of BT have been abolished by vagal maneuvers On the other hand His bundle electrograms in at least four cases have suggested an ectopic ventric ular origin *

As far as I can determine there has been only one other case of BT with QRS complexes of normal duration Pick and Langendorf[2] in their Fig 9 showed a paroxysmal BT with ■ precisely regular rate of 260 per minute in a child QRS duration was normal (0 10 sec) atrial activity was not identified and there were alternating T waves No further clinical details were provided

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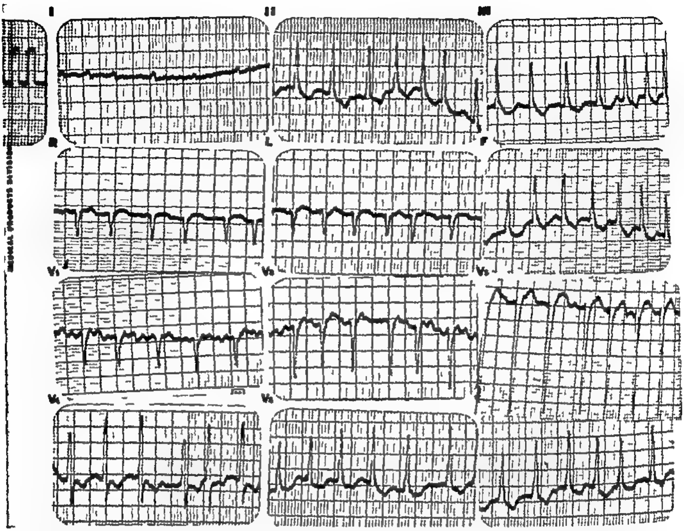

Fig 1 ECG obtained on admission Jan 26 1975 There is coarse atrial fibrillation with a rapid ventricular rate digitalis effect and probable biventricular hypertrophy QRS duration is 90 msec

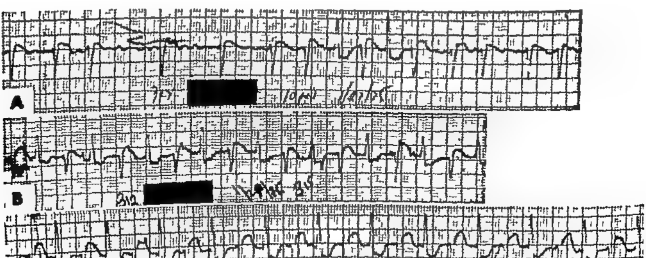

Fig 2 *A* *B* and *C* are recordings of V they were obtained several hours apart during the second hospital day Jan 27 1975 Strip *A* shows coarse atrial fibrillation with an irregular ventricular response and a brief run of BT with thin QRS complexes Strips *B* and *C* reveal persistent BT with a precisely regular ventricular rate of 180 per minute and QRS duration of 90 msec During the BT half of the QRS complexes are identical to those seen prior to its onset.

My patient had the usual clinical features of [including severe heart disease chronic atrial rillation digitalis toxicity and imminent ath Yet QRS duration remained normal roughout the tachycardia and there was no idence of intraventricular block. During the T half of the QRS complexes were identical to e existing ones suggesting that the arrhythmia as of supraventricular origin with alternating viation of intraventricular conduction Unfor nately a His bundle electrogram was not ob ained so that there is a theoretical possibility at my patient had an ectopic ventricular ythm with normal QRS contour[3] In any event e message is that BT with or without abnormal RS complexes usually occurs in very sick atients as a manifestation of digitalis toxicity

REFERENCES

1 Schwensen C Ventricular tachycardia as the result of the administration of digitalis, Heart 9 199 1922.
2 Pick A., and Langendorf R. Differentiation of supra ventricular and ventricular tachycardias, Prog Cardiovasc. Dis. 2 391 1960
3 Cohen S I Deisseroth, A., and Hecht H S Infra His bundle origin of bidirectional tachycardia Circulation 47 1-60 1973
4 Rosenbaum M B., Elizari, M V and Lazzari, J O The mechanism of bidirectional tachycardia Am Heart J 78 4 1969
5 Zimbdahl, W T and Townsend, C E Bidirectional ventricular tachycardia due to digitalis poisoning Am Heart J 47 304 1954
6 Reid D S Tynan, M Braidwood L and Fitzgerald G R Bidirectional tachycardia in a child A study using His bundle electrography Br Heart J 37 339 1975

The simultaneous occurrence of a ventricular septal defect and mitral insufficiency after myocardial infarction

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Development of a ventricular septal defect (VSD) or mitral regurgitation (MR) in a patient with acute myocardial infarction is usually suspected when the patient suddenly develops a systolic murmur associated with pulmonary congestion or systemic hypotension The diagnosis is important as both lesions are potentially correctable by surgery[1] Emergency surgery has been associated with disappointing results, however if the patient can be managed medically for 1 to 3 weeks or longer, results have been more favorable[2] The simultaneous occurrence of a VSD and mitral regurgitation after myocardial infarction is rare although its true incidence is probably not known We found only three cases reported[3-5] in the English literature thus the diagnosis and management are not yet well established The present report concerns the development of a VSD and mitral regurgitation in a 74 year old patient following myocardial infarction Apart from being rare, our case illustrates some interesting points (1) the diagnosis was made antemortem and confirmed postmortem (2) the diagnosis was made without resorting to left heart catheterization, and (3) medical management was successful in keeping the patient alive for 6 weeks and had she not refused surgery she would have otherwise been a candidate

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Case report

A 74 year old white woman was admitted to Barnes Hospital on Jan 20 1974 for right shoulder pain The patient had had asymptomatic hypertension for 12 years, treated with alpha methyldopa and hydrochlorthiazide Nine years prior to admission she had a cerebrovascular accident from which she completely recovered except for mild weakness of the right lower extremity There was no history of dyspnea on exertion, orthopnea ankle edema or paroxysmal nocturnal dyspnea On the evening prior to admission the patient developed severe right scapular pain associated with diaphoresis, nausea and vomiting which persisted for several hours. The patient was seen in the emergency department and immediately transferred to the cardiac care unit (CCU) with the diagnosis of acute myocardial infarction On admission the patient had normal sinus rhythm at a rate of 96 per minute and a blood pressure of 110/80 mm Hg There was no jugular venous distention The precordial maximal impulse was in the fifth intercostal space 1 cm lateral to the midclavicular line which was felt to be dyskinetic and associated with a presystolic impulse First and second heart sounds were decreased in intensity but otherwise normal Both third and fourth heart sounds were heard No murmurs were present Râles were heard bilaterally at the bases of the lungs. The electrocardiogram (ECG) on admission showed low QRS voltage marked left axis deviation with ST segment elevation and Q waves in V to V

Admitting laboratory data included normal urinalysis hemogram and serum electrolytes Chest x ray showed a heart of normal size and redistribution of blood flow to the apices of the lungs with tortuosity of the aorta Serum enzyme levels on admission were as follows creatine phosphokinase 83 serum glutamic oxalacetic transaminase 65 lactic dehydrogenase 139 these reached peak levels of 1 500 2,900 and 1 100 respectively in the next 3 days Two days after admission the patient had another severe attack of chest pain followed by hypotension (80/60 mm Hg) and urine output of less than 15 ml per minute Because of the deteriorating hemodynamic status, a Swan Ganz catheter was placed in the pulmonary artery and an arterial catheter into the brachial artery The various hemodynamic parameters obtained are shown in Table I

The patient was treated with intravenous furosemide (?00 mg) and continued for the next few days with the dose regulated to keep the pulmonary ...

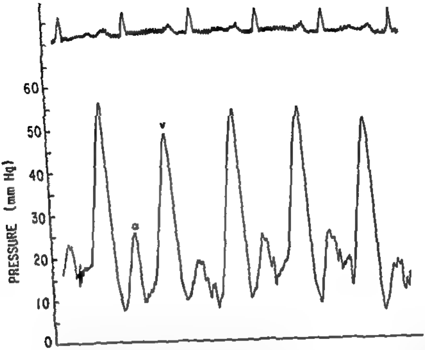

Fig 1 This figure illustrates the ECG (top tracing) and pulmonary artery occlusive pressure (bottom tracing) obtained via a Swan Ganz catheter from the patient on her second admission to the CCU The marked increase of v waves over a waves highly suggests mitral insufficiency

Table I Results of cardiac catheterization performed on the first admission

	Systolic and diastolic pressures (mm Hg)	*Mean pressure (mm Hg)*
Right atrium (RA)		12
Right ventricle (RV)	45/7	
Pulmonary artery (PA)	45/?2	30
Pulmonary artery occlusive pressure (PAOp)	a = 22 v = 19	18
Brachial artery	82/60	67

Right-s ded pressures w re btai ed via Swan G nz c th ter a ref rs to peak p essure during trial sy tole and to peak pressu during atrial diastole The m an p lmonary artery occlusi e pressure is le ated, ind cating l ft ventricular f ilure how v r the ormal conto r s l des any signifi ant mit al regurgitati n

Table II Results of cardiac catheterization performed on the second admission to the CCU

	Systolic and diastolic pressures (mm Hg)	*Mean pressure (mm Hg)*	*Po_2 (mm Hg)*
Right atrium (RA)	a = 10 v = 8	8	29
Right ventricle (RV)	50/5		45
Pulmonary artery (PA)	50/25	33	48
Pulmonary artery occlusive pressure (PAOp)	a = 22 v = 50	25	
Brachial artery	80/60	67	56

There is now a large w e in keeping with m tral regurgitation. R ght ded pressures were btained ia a Swan-Ganz athet r a refers to pe k pressure during atrial sy tole a d v to peak p essure during atrial diastol

between 16 and 20 mm Hg. Chest x ray showed marked pulmonary vascular ongestion Twenty four hours later because of the persistent hypotension isoproterenol (2 mg per 500 ml) and Levophed (8 mg per 500 ml) by continuous infusion were administered digoxin was also given intravenously in 0.5 mg doses for a total of three and the patient was maintained on 0.25 mg. per day The patient responded with a systolic blood pressure of 1?0 mm Hg and a urine output of 1400 ml. per ?4 hours. The Swan Ganz and intra arterial catheters were removed and the isoproterenol was discontinued on the fifth day On the tenth day the patient was transferred out of the CCU to the regular ward She continued to have evidence of congestive heart failure however despite sodium restriction diuretics, and digoxin Eight days later oliguria hypotension and bilateral pleural effusions developed and she was transferred back to the CCU On arrival, she was noted to have a pansystolic murmur at the left sternal border radiating into the axilla which was not present previously Catheters were again placed in the pulmonary and brachial arteries. In addition to hemodynamics blood samples

were obtained from the right atrium (RA) right ventricle (RV) pulmonary artery (PA) and the brachial artery and analyzed for O_2 saturation The results are shown in Table II Clinically because of the hypotension oliguria and the development of a murmur it was assumed that the ventricular septum had ruptured The VSD was confirmed by the increased O saturation in the RV and PA but because of the large v waves (shown in Fig 1) mitral regurgitation was also assumed to be present The patient received intensive therapy with intravenous furosemide and isoproterenol to maintain blood pressure and adequate urine output Hemodynamic status was continuously monitored and the pulmonary artery occlusive pressure was kept around 20 mm Hg Systemic heparinization was initiated and maintained with the hope of preventing venous thrombosis The subsequent hospital course was further complicated by urinary tract infection and pneumonia Hemodynamic monitoring was maintained for 8 days and the patient was stabilized on digoxin (0 25 mg per day) and furosemide (100 mg per day) The patient was approached regarding surgery but refused on the advice of her family She was transferred to the general ward and did well for 5 weeks then her condition again deteriorated with increasing failure and she died At autopsy the heart weighed 300 grams. The coronary arteries showed marked atherosclerosis with complete occlusion of the left main and the left anterior descending coronary arteries by recent thrombi The lumens of the left circumflex and right coronary artery were markedly narrowed (> 80 per cent) but there was no evidence of recent thrombi. The anterior wall of the left ventricle showed an area of thinning and fibrosis together with recent necrosis which extended into the ventricular septum In the thinnest portion of the septum near the apex there was an acquired septal defect of 0.5 cm An old fibrotic scar with recent necrosis and healing was seen in the posterior wall of the left ventricle involving the posterior papillary muscle The lungs showed acute chronic congestion pleural effusion organizing pulmonary emboli and acute bronchopneumonia

Discussion

Only three cases of VSD and MR occurring after myocardial infarction have been reported and only one was diagnosed antemortem [5] In our case the diagnosis was established by a relatively simple procedure the insertion of a balloon tipped catheter to the right side of the heart The oxygen saturation was determined in the RA RV and PA, which showed a step up in O_2 saturation at the ventricular level indicating a VSD The PAOp tracing is a reflection of the left atrial pressure, and the giant ' v' waves reflected re... gitation into the left atrium during systole B... VSD and MR were confirmed postmortem. Th... it was possible to diagnose VSD and MR witho... left heart catheterization, which could be a haz... dous procedure in this situation

Surgery has been shown to be helpful wh... mitral regurgitation or VSD occurs alone parti... cularly if performed a few weeks after infarctio... It is possible that surgery may be helpful wh... both lesions are present if recovery is possible fo... 2 to 3 weeks The fact that this patient did survi... for 6 weeks emphasizes the importance of mak... the diagnosis and maintaining medical treatm... Furthermore, we feel that hemodynamic moni... toring of therapy is essential and provides for more rational comprehensive management Th... mean pulmonary artery occlusive pressure wa... maintained around 25 mm Hg, with fluids a... diuretics as needed The systolic blood pressure was maintained between 85 and 100 mm Hg with Levophed and isoproterenol It may be argued that the potential risk of increasing myocardial necrosis with these agents would contraindicate their use, but it was necessary to maintain the systolic pressure above 60 mm Hg Dopamine which is now available, would probably have bee... a better agent

REFERENCES

1 Buckley M J Mundth E D Daggett W M et al. Surgical therapy for early complications of myocardial infarction Surgery 70 814 1971
2 Giuliani E R Danielson G K Pluth J R et al. Postinfarction ventricular septal rupture Surgical considerations and results Circulation 49 455 1974
3 Rawlins M D Mendel D and Braimbridge M V Ventricular septal defect and mitral regurgitation secondary to myocardial infarction Br Heart J 34 32... 1972
4 Ventricular septal defect and mitral regurgitation secondary to myocardial infarction Br Heart J 35 1... 1973
5 Skoulas A and Beier R L Dissecting perforation of infarcted interventricular septum with associated posterior papillary muscle involvement Am J Med 43 461 1967

linical pathologic conference

besity football, dog days and siriasis deadly combination

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se presentation

The patient was a 15 year old obese boy (body ight 230 lb) He was in apparent good health til August 18 1975 when after one hour of his st football practice for the season he suddenly lt sick vomited and collapsed On arrival at the nergency room of a nearby hospital the temper ture was 98 8 F the pulse rate 100 per minute he respiratory rate 24 per minute and his blood ressure 148/76 mm Hg He exhibited violent and busive behavior for which he received diazepam nd chlorpromazine

His physical examination was unremarkable except for diminished deep tendon reflexes The urine was cloudy and gave a 4+ test for protein and a 3+ test for blood The sediment contained no red cells The hematocrit was 45 per cent the white blood cell count was 8 600 with 36 per cent neutrophils 5 per cent band forms and 59 per cent lymphocytes The platelets were described as adequate in the peripheral blood smear The prothrombin time was 28 seconds (control 12 5) The blood urea nitrogen was 42 mg per cent the sodium 143 mEq potassium 4 4 mEq chloride 101 mEq and the carbon dioxide 26 mEq per liter His total serum bilirubin was 1 9 mg per cent the alkaline phosphatase 60 I U the lactic dehydrogenase (LDH) 760 I U (normal 75 to 175 I U per liter) and the glutamic oxalacetic transaminase (SGOT) 390 I U (normal 35 to 175 I U per liter) The chest roentgenogram was normal

The patient after hospitalization developed a temperature of 103 F He remained agitated developed guaiac positive emesis and became hypotensive Metaraminol bitartrate acetylsalicylic acid and diazepam were administered During the next 20 hours his mental status fluctuated The urine output decreased in volume and later in the day he became anuric On the third hospital day his mental status had deteriorated to a state of stupor A lumbar puncture showed an opening pressure of 230 cm of H_2O and the cerebrospinal fluid contained 20 4 mg per cent of protein and 122 mg per cent of glucose There were no white blood cells but red blood cells 108/mm were present A specimen of arterial blood drawn with the patient breathing room air revealed a partial pressure of oxygen of 40 mm Hg a partial pressure of carbon dioxide of 42 mm Hg and a pH of 7 06 His condition improved somewhat after he was given oxygen by mask and intravenous sodium bicarbonate The patient was then transferred to St Luke s Episcopal Hospital

On admission he was comatose His temperature was 99 F the pulse rate 120 per minute and the respiration rate 16 per minute His blood pressure was 150/80 mm Hg His pupils were equal and reactive to light A fundoscopic examination was normal The neck was supple the lung fields were clear by auscultation and the heart sounds were normal The abdomen was soft and the urinary bladder empty The deep tendon reflexes were decreased and the plantar response was flexor The extremities showed oozing of blood from venipuncture sites

He had a hematocrit of 39 per cent the white

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Table I Syndromes of heat illness

Heat cramps	Due to loss of body salt through sweating. Characterized by painful contracture of voluntary muscles. Body temperature is normal or slightly subnormal
Heat exhaustion (heat prostration)	Due to water and salt depletion, hypovolemia. Characterized by progressive lassitude followed by headache, vomiting, tachycardia and hypotension. Body temperature may be normal, slightly lowered or raised
Heat stroke (heat pyrexia, sunstroke)	Due to overheating of the body in addition to above. A life threatening medical emergency, usually exercise induced, characterized by: 1 severe CNS disturbances, 2 hyperpyrexia (41–43 C), and 3 hot dry skin, pink or ashen in color

blood cell count was 15,200/mm^3 with 95 per cent neutrophils and 5 per cent lymphocytes. The platelet count was 30,000/mm^3. The prothrombin time was greater than 90 seconds (control 11 seconds) and partial thromboplastin time was greater than 110 seconds. The plasma fibrinogen was 0 and the fibrin split products were strongly positive in a 1:16 dilution. The blood urea nitrogen was 58 mg per cent, the creatinine 10.3 mg per cent, calcium 6.9 mg per cent, uric acid 21.9 mg per cent, albumin 3.2 G per cent and the glucose 305 mg per cent. The serum sodium was 128 mEq, potassium 5.0 mEq, chloride 87 mEq and carbon dioxide 12 mEq per liter. Arterial blood gases drawn at an unknown oxygen tension showed the partial pressure of oxygen to be 109 mm Hg, the partial pressure of carbon dioxide was 28.9 mm Hg and the pH 7.24. The SGOT was 15,531 I.U. and the creatine phosphokinase (CPK) was 20,100 I.U. An electrocardiogram showed atrial fibrillation with a rapid ventricular response.

The patient was given intravenous sodium bicarbonate, calcium gluconate, heparin and cryoprecipitate in preparation for the creation of an arteriovenous shunt for hemodialysis. The following day, his plasma fibrinogen level was 123 mg per cent, but he continued to ooze from the venipuncture sites. The morning of August 22 the patient suffered a massive epistaxis, cardiac arrest followed, and he could not be resuscitated.

Clinical discussion

DR BARCENAS: This 15 year old boy collapsed suddenly and presented a clinical syndrome consisting of fever, acute mental confusion progressing rapidly to coma, a bleeding disorder compatible with disseminated intravascular coagulation (DIC), hemolysis, rhabdomyolysis and acute renal failure. It started after his first football practice for the season, and led to his death four days later.

The patient's symptomatology may be found in three types of clinical situations: infections, drug abuse, and certain metabolic derangements. Among the infectious processes, neurotrophic virus encephalitis, tetanus, leptospirosis and meningococcal meningitis can present with the composite of coma, rhabdomyolysis, renal failure and DIC.[1] The apparent good health of the patient prior to his acute illness, as well as the lack of exposure to any known microbial infective agents, make infection an unlikely diagnostic possibility. Self administered amphetamines, lysergic acid diethylamide (LSD) or heroin, and withdrawal from alcohol can also produce the clinical picture under consideration,[3] but we have no reason to suspect drug abuse. Poisonous snake bites (e.g. *Crotalus Adamanteus* which is found in this area of the country) may induce DIC and rhabdomyolysis, and conceivably could lead to acute renal failure and coma.[4] But no one had reported the sighting of a rattle snake on or near the football field.

The clinical diagnosis that best explains this young man's illness is a metabolic derangement known as heat stroke induced by exercise. Heat illness is thought to occur mainly in tropical countries; however, it causes close to 4,000 deaths every year in the more humid areas of the United States.

The body temperature is a composite of (1) the environmental temperature and humidity, (2) the body production of heat, and (3) the loss of heat from the body. The body heat gain is markedly increased by a high environmental temperature and can be as much as 150 KCal/hour when exposed to direct sunlight at 35° C. Hard physical work will also induce hyperthermia from heat generated by metabolic processes. Heat production can be as high as 600 to 900 KCal/hour

ble II Predisposing factors of heat stroke

nmon to both non exercise–induced and exercise–induced arieties
High ambient temperature and humidity
Drugs that *increase* heat production (thyroid extracts amphetamines, lysergic acid diethylamide)
Drugs that *decrease thirst* (haloperidol) and *sweating* (antihistamines anticholinergics phenothiazines benztropine mesylate propranolol)
on exercised induced variety
Chronic illness especially congestive heart failure alcoholism and malnutrition
Sweat gland dysfunction (scleroderma cystic fibrosis)
xercise-induced variety
Inadequate acclimatization
Obesity
Potassium and salt depletion

uring maximal work The body heat loss is ccomplished normally by radiation conduction nd convexion If the environmental temperature s above 30 C absorption of infrared energy rom the environment approaches emission and heat dissipation by radiation becomes impossible Once the outside temperature equals or exceeds the body temperature heat can be lost only by evaporation of sweat In order to lose one calorie the body must evaporate (not only produce) 1 72 ml. of sweat *The recorded temperature of the day the patient collapsed was 37° C and the environmental humidity was 97 per cent* It is easily understandable how the performance of strenuous exercise under those conditions led to heat induced illness in this patient as the heat generated during exercise could not be dissipated adequately

Heat illness can be manifested in three clinical syndromes (Table I) *Heat cramps and heat exhaustion* are milder and commoner forms of heat illness I shall now concentrate on a discussion of the more severe form that of *heat stroke* which is an extreme medical emergency characterized by hyperpyrexia (> 41 C) delirium coma and anhydrosis There are two clinical types of heat stroke (1) non exercise induced occurring in older individuals with underlying cardiovascular disease exposed to high ambient temperatures and who are salt and water deprived and (2) exercise induced occurring in younger healthy individuals who are unable to dissipate the heat produced by physical exercise in a hot environment To the second type of heat stroke our patient belonged I believe

Table III Complications of heat stroke

1 *Central nervous system damage* Agitation psychotic behavior coma
2 *Acute renal failure* 5% in non exertional type and 30% in exertional type heat strokes
3 *Rhabdomyolysis* Only in exertional type heat stroke
4 *Coagulation disorders* Disseminated intravascular coagulation due to impaired liver function and endothelial cell damage
5 *Hepatocellular necrosis*
6 *Myocardial necrosis*
7 *Electrolyte and acid base disturbances*
Hypernatremia hypo hyperkalemia hypocalcemia hyperphosphatemia hyperuricemia *Respiratory* alkalosis in non-exertional type and lactic acidosis in exertional type heat stroke

Table IV Management of heat stroke patients

1 Start an intravenous line immediately
2 *Intubate the patient if comatose or convulsing*
3 *Cool patient to 39 3 C in 60 minutes or less in ice water*
4 Obtain complete blood counts coagulation indices urinalysis and blood electrolytes urea nitrogen creatinine and *repeat at intervals if necessary*
5 Administer chlorpromazine parenterally at the start of body cooling process to prevent shivering
6 Support the cardiovascular system avoiding the use of norepinephrine Administer crystalloids carefully to prevent overloading
7 Insert bladder catheter and maintain a urine output greater than 30 ml /hr with mannitol or furosemide
8 If DIC is present consider heparin therapy
9 If renal failure supervenes, early hemodialysis should be instituted
10 Monitor acid base status frequently Consider sodium bicarbonate administration if blood pH is very low

Factors that predispose to heat stroke are summarized in Table II I should point out that heat loss through the skin occurs by vasodilatation The increased blood flow in the skin and probably also in the skeletal muscles will impose marked demands upon the performance of the cardiac muscle It is then understandable that in the first type of heat stroke survival is critically dependent on an intact cardiovascular system that is capable of increasing the cardiac output to meet the elevated circulatory demand [4]

In the exercise induced variety the role of potassium depletion has been emphasized by Knochel and associates Studies done on recruits undergoing physical conditioning show that sweat losses and lack of adequate volume replace

Fig 1 Hemorrhagic necrosis of the anterior papillary muscle of the left ventricle Note fragmentation of individual myocardial fibers and flooding of the interstitium by extravasated red blood cells (Hematoxylin and eosin stain ×240)

ment lead to secondary aldosteronism which in turn induces renal losses of potassium and eventual potassium depletion This predisposes to rhabdomyolysis and heat stroke by inhibiting the vasodilatation of exercising skeletal muscle [8]

The case under discussion represents a classic example of the various serious complications of exercise induced heat stroke (Table III) In this type of heat stroke agitation confusion and psychotic behavior are commonly present and can be misleading Seizures are common The CSF is usually normal as well as the EEG In the majority of organ systems the damage is secondary to the hyperpyrexia The acute renal failure is secondary to rhabdomyolysis and dehydration with an acid urine Hyperuricemia has also been implicated in the pathogenesis but its exact role is not clear [11]

Muscle destruction has been observed only in the exercise induced heat stroke and is responsible for the marked electrolyte abnormalities commonly encountered These include hyperkalemia hyperuricemia and hyperphosphatemia together with hypocalcemia Liver damage and myocardial necrosis are frequently found and are believed to be secondary to direct thermal injury Transmural myocardial infarction has been described in the presence of normal coronary arteries

The patient presented with a bleeding tendency and the laboratory findings are suggestive of severe ongoing DIC This is a well recognized complication of heat stroke and is induced by widespread endothelial cell injury [1,2] Decreased clotting factor production by the liver, as well as enhanced fibrinolysis due to exercise in the heat are also responsible for the bleeding abnormalities observed in this condition The patient developed a severe metabolic acidosis which was almost certainly due to lactic acid accumulation Patients with non exercise induced heat stroke generally develop a respiratory alkalosis as a consequence of hyperventilation Individuals with exertion induced heat stroke may display the same abnormalities at first but lactic acidosis usually supervenes and may become worse as the hypotension is corrected and hydrogen ions are washed out from skeletal muscle [7]

We do not know how the body temperature was determined in this patient but if the oral temperature is the one that was recorded hyperventilation may account for the low value obtained

Success in the management of heat stroke is dependent on the immediate lowering of the temperature and effective support of the vital organ systems (Table IV) It should be emphasized that as cooling is achieved peripheral vasoconstriction will return a significant amount of blood to the central circulation and sudden fluid expansion may lead to pulmonary edema Measures to prevent heat stroke have been recently published [3] and will not be discussed

In summary I believe this patient had exertion induced heat stroke with all of its major

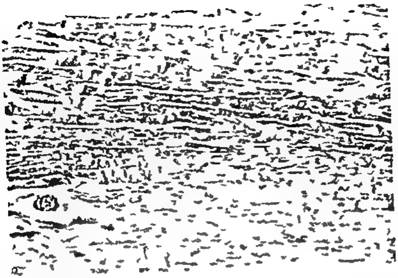

Fig 2 Myofibrillar degeneration and interstitial edema Note uneven staining of individual fibers and the presence of numerous irregularly spaced transverse contraction bands (Hematoxylin and eosin stain ×240)

Fig 3 A bloodless glomerulus with apparent hyperplasia of the juxtaglomerular apparatus (*straight arrow*) and focal mesangial proliferation (*curved arrows*) (Hematoxylin and eosin stain ×600)

complications The immediate cause of death is not apparent but may have been secondary to aspiration of blood into the trachea

Autopsy findings

Dr Hoeffler This patient had generalized soft tissue hemorrhage particularly in the diaphragm the periaortic and retroperitoneal connective tissue and hemorrhagic necrosis of the left psoas muscle A moderate amount of altered blood was also present in the stomach the upper small intestine and the ascending colon In addition punctate hemorrhages were also present in the pleurae the epicardium and the endocardium There was at the time of autopsy no histopathologic evidence of DIC nor evidence of aspiration of blood

The most striking findings were in the heart kidneys and the liver The heart weighed 410 G but this need not signify cardiac hypertrophy As noted above the patient was quite an obese individual (230 lbs) and this would account for in part at least the increased heart weight An area of hemorrhagic necrosis was present in the anterior papillary muscle of the left ventricle (Fig 1) Elsewhere in the heart the myocardium showed

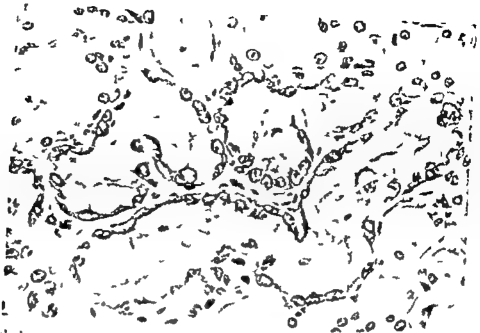

Fig 4 Acute tubular necrosis Note nuclear pleomorphism of the degenerating and regenerating tubular epithelium (Hematoxylin and eosin stain ×600)

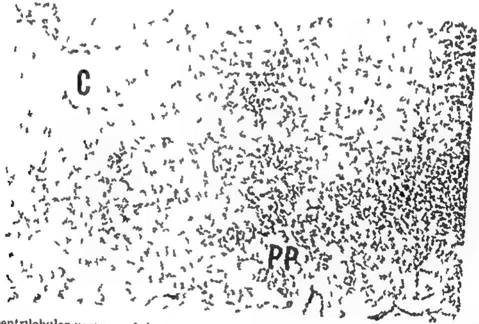

Fig 5 Severe centrilobular necrosis of the liver Note that nearly all the hepatocytes surrounding the dilated central vein (*C*) undergo lytic degeneration with only some periportal (*P P*) hepatocytes surviving (Hematoxylin and eosin stain ×80)

multifocal subendocardial wavy fibers and myofibrillar degeneration (Fig 2)

The kidneys were somewhat pale and edematous and together weighed 495 G Most of the glomeruli were bloodless but otherwise unremarkable (Fig 3) Extensive tubular changes were observed The proximal tubules were dilated and lined either by necrotic degenerated epithelium or pleomorphic regenerating epithelium with large bizarre nuclei (Fig 4) An occasional mitotic figure was present in the tubular epithelium Many of the distal and collecting tubules contained myoglobin and red cell casts

The liver showed widespread and severe centrilobular necrosis and in some areas panlobular necrosis (Fig 5) Most of the central veins and some of the portal veins were dilated A mixed cell inflammatory infiltrate was present predominantly in the periportal areas where most of the surviving hepatocytes were found There was some evidence of regenerative activity as indicated by liver cell cords of more than one cell thickness and the presence of multinucleated hepatocytes (Fig 6) The oil red O stain showed that most of the necrotic centrilobular hepatocytes contained fat Bile stasis was minimal

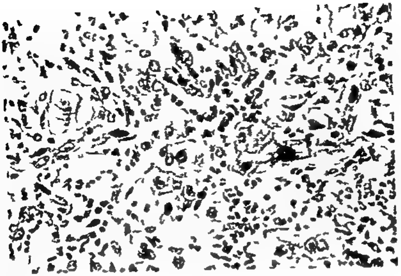

Fig 8 Higher magnification view of the periportal hepatocytes and the mixed cell inflammatory infiltrate (Hematoxylin and eosin stain ×600)

The lungs and other visceral organs showed vascular engorgement only The brain had no grossly discernible abnormality and the only significant histologic finding was minimal neuronal degeneration and focal hemorrhage in the sections taken from the posterior hypothalamus areas

In summary the pertinent autopsy findings *soft tissue hemorrhages rhabdomyolysis of the psoas muscle focal hemorrhagic necrosis of the myocardium and myofibrillar degeneration acute renal tubular necrosis and massive centrilobular hepatic necrosis* are characteristic of *heat stroke*

General comment

Dr. Lie Heat stroke is not a medical emergency that one would expect to encounter only in the perennial hot and humid southern India or in the underground gold mines of South Africa Nor is it peculiar to military recruits unaccustomed to the stress of physical exertion

Although the now classical work of Malamud and associates was a comprehensive clinicopathologic study of 125 fatal cases of heat stroke in soldiers undergoing intensive training There have been also several large scale studies of civilian heat stroke casualties

Strenuous football practice or game constitutes a health hazard especially for an obese individual so it would appear Some years ago Sohal and associates from our neighboring state of Louisiana reported the death of a 16 year old boy under similar circumstances

Hemorrhagic diathesis and parenchymal tissue injuries observed in the vital organs of heat stroke victims have all been attributed to the direct effects of hyperpyrexia [1] and the general state of hypoxia secondary to shock is doubtless an important contributory factor While damage to virtually every organ system of the body has been described the extent and severity of tissue injuries vary considerably in different individuals And in the case under discussion the most seriously damaged organs were the liver kidneys and the heart

Hepatocellular damage is not an inevitable consequence of heat stroke nor irreversible once developed In the larger series reported by Malamud and associates there was no evidence of damage to liver parenchymal cells in patients who had died within 30 hours and the degree of damage ranged from moderate to severe in the 12 patients in whom necrosis was present all 12 patients had survived from 31 to 276 hours after the onset of heat stroke In the smaller series reported by Kew and associates only about 10 per cent of patients had severe liver damage that may have contributed to fatal outcome Hepatic injury was mild or moderate in the remaining 90 per cent of patients and could be detected only on biochemical testing or liver biopsy The pathologic changes consisted of congestion centrilobular degeneration or necrosis of hepatocytes and cholestasis In the patients who survived the histologic and biochemical abnormalities were completely reversible

The kidneys usually are hyperemic in heat

stroke irrespective of the duration of illness, and subcapsular and pelvic mucosal hemorrhages are not uncommon Structural changes sufficiently pronounced to qualify as acute tubular necrosis (lower nephron nephrosis, "hemoglobinuric nephrosis) are observed in more severely affected patients and those who had survived longer than 24 hours[1, 1] While rhabdomyolysis and hemolysis are important contributing factors acute renal failure of heat stroke is indistinguishable histologically from acute tubular necrosis of shock from other causes[4, 5]

Finally in regard to injuries to the heart in heat stroke Kew and associates[16] found clinical evidence of cardiac damage in 17 of 26 Bantu goldminers Myocardial injury was diagnosed on the basis of serum LDH isoenzyme patterns and electrocardiographically A good (75 per cent) correlation was found between the LDH-1 isoenzyme elevation and ECG evidence of cardiac damage Focal hemorrhagic necrosis and myofibrillar degeneration, as we have observed in this case (Figs 1 and 2), were found by Malamud and associates[1] to be present in one third of their patients who died within 24 hours, and in one half of those who survived a longer period after developing heat stroke Myofibrillar degeneration (Fig 2) is a nonspecific morphologic marker of cardiac injury, and heat stroke is yet another entity to be added to the expanding list of diverse conditions in which myofibrillar degeneration is known to occur

The enjoyment of sporting activities should not be marred by the tragic loss of a youthful life, however infrequent this might be Both the lay public and the medical profession alike should be constantly reminded of the seriousness of heat stroke and especially that heat stroke is a preventable disease[13, 18, 0]

REFERENCES

1 Rapaport S I Defibrination syndromes *in* Hematology Williams W ed New York 1972 McGraw Hill Book Company Inc p 1234

2 Rowland L P and Penn A S Myoglobinuria Med Clin North Am **56** 1233 1972

3 Grossman R A Hamilton R W and Morse E M et al Non traumatic rhabdomyolysis and acute renal failure N Engl J Med **291** 807 1974

4 Weiss H J Allan S and Davidson E et al Afibrinogenemia in man following the bite of a rattle snake (Crotalus Adamanteus) Am J Med **47** 625 1969

5 Schuman S H Patterns of urban heat wave deaths and implications for prevention Data from New Yor St. Louis during July 1966, Environ. Res. 5 59 19

6. Gilat, T., Shibolet, R., and Sohar E. The mechanis heat stroke, J Trop. Med. Hyg **66** 204 1963.

7 Knochel, J P., Environmental heat illness, Arch I Med. **133** 841 1974.

8. O Donnell, T F., Jr., and Clowes, C H A, Jr circulatory abnormalities of heat stroke, New Engl Med. **287** 734 1972.

9. Knochel, J P., Dotin, L. N., and Hamburger R. Pathophysiology of intense physical conditioning in a climate I Mechanism of potassium depletion, J Cl Invest. **51** 242, 1972.

10. Knochel, J P., and Schlein E. M On the mechanism rhabdomyolysis in potassium depletion J Clin I **51** 1750 1972.

11 Knochel J P., and Dotin L. N., and Hamburger R. Heat stress, exercise and muscle injury Effects on u metabolism and renal function Am Intern Med 81 1974

12. Weber M B and Blakely J A The hemorrha diathesis of heat stroke A consumption coagulopa successfully treated with heparin Lancet 1 1190, 1969

13. Knochel J P Dog days and siriasis, J.A M A. 233 1975

14 Kumar P Rathore C K and Nagar A M et Hyperpyrexia with special reference to heat stroke A analysis of 108 cases, J Indian Med Assoc. 1964

15 Kew M C Abrahams, C Levin N W et al The effe of heat stroke on the function and structure of th kidney Q J Med **36** 277 1967

16. Kew M C Tucker R B K and Bersohn I et al The heart in heatstroke Am Heart J **77** 324 1969

17 Kew M C Bersoh I and Seftel H et al. Liver damage in heatstroke Am J Med **49** 192 1970

18. Stonehill R. B and Keil P G Successful preventive medical measures against heat illness at Lackland Air Force Base Am J Public Health **51** 586 1961

19 Minard D Prevention of heat casualties in Marine Corps recruits Period of 1955 1969 with compari incidence rates and climatic heat stresses in othe training categories Milit Med **126** 261 1961

20 O Donnell T F Jr Medical problems of recruit training A research approach U S Navy Med **58** 28 1971

21 Malamud N Haymaker W and Custer R P Heat stroke A clinicopathologic study of 125 fatal cases, M Surg **99** 397 1946

22 Gauso H and Meyer K A Heat stroke Report o hundred and fifty eight cases from Cook County I tal Chicago Am J Med Sci **154** 554 1917

23 Sohal R S Sun S C and Colcolough H L et al Heat stroke An electron microscopic study of endothelial cell damage and disseminated intravascular coagulation Arch Intern Med **122** 43 1968

24 Dunhill M S A review of the pathology and pathogenesis of acute renal failure due to acute tubular necrosis J Clin Pathol **27** 2 1974

25 Dunhill M S and Jerrome D W Renal tubular necrosis due to shock Light and electron microscope observations J Pathol **118** 109 1976

26 Reichenbach D D and Benditt E P Catecholamines and cardiomyopathy The pathogenesis and potential importance of myofibrillar degeneration Human Pathol **1** 125 1970

nical evaluation of aortic and mitral valve ostheses

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placement of diseased aortic and/or mitral lves with prosthetic devices began on a wide read basis only as recently as the 1960 s Since ntinuing follow up of the thousands of patients volved will be primarily the responsibility of the neral internists and cardiologists who recom ended valve replacement these physicians must prepared to evaluate these patients with mple clinical measures

Too often it is considered that a patient with vere valvular heart disease is cured once his carred valve is successfully replaced with a pros hetic device However once the patient has a ardiac valve prosthesis in place he is in fact ommitted to a lifetime of careful medical management for he is subject to innumerable omplications Also if the patient lives long nough the prosthesis will almost certainly have to be replaced since few man made things will last 40 or 50 years

In this report some of the problems that the physician may encounter while following patients with aortic and mitral valve prostheses are discussed Emphasis is placed on a simple clinical approach to these problems. It should be noted that although many types of prosthetic valves are currently available the complications and natural histories are similar for most of them

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Hemodynamic changes following aortic and mitral valve replacement

Proper evaluation of patients with valve prostheses requires (1) knowledge of the hemody namic changes to be expected following the oper ation and (2) the natural history of such patients without complications due to valve replacement

Mitral valve replacement Replacement of the mitral valve with a prosthesis is usually done in instances of severe mitral insufficiency or a severely calcified stenotic valve for which satis factory commissurotomy is not possible The immediate surgical mortality rate for mitral valve replacement usually ranges upward from 5 per cent depending mainly on the surgeon perform ing the operation An operative mortality rate of approximately 2 per cent has been reported for certain selected patients

Immediately following successful operation in patients with mitral insufficiency the cardiac output and left and right ventricular stroke work rise markedly and left atrial and pulmonary arterial and venous pressures are greatly decreased These beneficial changes are still present 1 year or more after successful operation and valve function [1]

Mitral valve replacement for predominant mitral stenosis is followed by an increase in cardiac output increase in left and right ventric ular stroke work and as favorable a response as for mitral insufficiency In some instances surgery is followed by no decrease in pulmonary vascular resistance Also left atrial pressure does not always decrease consistently The Starr Edwards prosthesis (ball in case) has a tendency to produce a diastolic gradient between the left

atrium and the left ventricle[8] The low profile, tilting disc prostheses e g Bjork Shiley valve, produces less obstruction than the ball[8]

Long term follow up of patients with mitral valve prostheses shows that although the post operative increases in cardiac output and decreases in pulmonary capillary wedge pressures and pulmonary vascular resistance still exist hemodynamic phenomena may become abnormal during exercise[4] Some of the abnormalities may be related to the myocardial disease itself or to a persistently abnormally high left atrial–left ventricular pressure gradient

Aortic valve replacement Replacement of the aortic valve in patients with aortic stenosis is followed immediately by an increase in cardiac output with a marked reduction in left ventricular pressure and left ventricular stroke work The left ventricle becomes much more efficient Correction of *aortic regurgitation* by valve replacement is followed by an increase in forward stroke volume associated with a decrease in left ventricular end diastolic pressure and an increase in systemic arterial pressure

In patients with more than one valve prosthesis the initial and late beneficial postoperative hemodynamic changes reflect the hemodynamic disturbances produced by the preoperative cardiac valve lesions

History taking and symptoms Successful valve replacement should result in improvement in the symptoms of cardiac failure and dysfunction and general well being of the patient The experienced clinician readily recognizes these changes of improvement Thus after the immediate postoperative period failure of the patient to improve clinically should alert the physician to a possible dysfunction of the valve prosthesis or a serious surgical complication A sudden departure from good health is more likely to represent mechanical dysfunction of the prosthetic valve rather than progression of cardiomyopathy electrolyte disturbances, or other abnormal disease states

Also, the early symptoms of valve dysfunction may be vague and unimpressive Therefore the patient should be followed meticulously Symptoms of systemic and pulmonary embolism hemolysis, and anemia or infection may be subtle and may require detailed history taking Intermittent angina pectoris may be caused by intermittent aortic prosthetic valve dysfunction

Finally, the physician must be fully aware th serious mechanical problems of valve pro the may exist without changes in patient sy tology

Expected auscultatory manifestations in pati with mitral and aortic valve prostheses

Mitral valve Mitral valve prostheses produc closing sound' beginning 0 06 to 0 08 sec following the onset of the QRS complex[10] Occ sionally, a few sounds of less intensity follow Th opening sound" of the mitral valve prosthes follows the second heart sound by 0 07 to 0 second Other diastolic sounds related to at systole may be heard

Tilting disc prostheses (Bjork Shiley, etc) produce softer sounds than the ball cage type a the closing sound may be no louder than a norma second heart sound The tilting disc valve (Bjork Shiley and Wada Cutter) and the Mag vern ball valve usually produce faint murmurs o incompetence because of small inherent regurgi tation

Frequent auscultation of the patient with prosthetic valve by the same physician is nec sary to detect early any subtle changes in val sounds which reflect malfunction and complica tions such as infection or thrombosis on the valve Careful descriptions of the valve sounds should be recorded at each visit to ensure reliable compari sons

Aortic valve Aortic valve prostheses are usually of the basic ball in cage' or tilting disc type The nontilting disc valves are encountered infrequently The ball in cage prosthesis produces a sharp opening sound which follows the first heart sound (S_1) by an average interval of 0 07 second and the rise of the carotid pulse by 0 02 second[9,1] The second heart sound (S_2) is also a sharp short closing sound which occupies the position of the aortic second sound The quality of these sounds varies with the material of which the ball and cage are constructed

Graphic recordings and x ray Phonocardiograms may be used in conjunction with but not as a substitute for careful auscultation to follow the sounds of prosthetic valves Particular attention must be given to notation of the details of the technique of recording e g placement of microphones fidelity of recording paper speed and the like to minimize variations due to recording

nique Measurements of certain time inter should be made such as the S_2–OC (opening k) and Q S_1 intervals These intervals vary in ation depending on the function of the valve sthesis Long Q S_1 intervals (normal 0 04 to 3 sec) are associated with interference with oper seating of valve poppet The S_2–OC erval is usually 0 07 to 0 15 second and abnor lly short or long intervals may be associated th prosthetic valve dysfunction (see below) iations in amplitude of the prosthetic valve unds and in ratios of these amplitudes e g rtic opening to aortic closing sounds do not em practical for the physician who does not ve highly sophisticated recording equipment d technique

Serial chest x rays fluoroscopy and when ossible cinefluoroscopy are very helpful in eval ating the state of function of cardiac valve rostheses The position of the prosthesis in arious oblique views and the motion of the valve ng and disc or poppet (if the latter are radio aque) may serve to detect improper anchoring of he valve ring or abnormal motion of the poppet r disc A routine EPA chest radiograph with an xposure of 1/30 of a second with high penetra ion may detect abnormal valve motion Dehis ence of 30 per cent or more of the prosthetic ring s required before abnormal motion will be appar nt i e the film will show the fixed portion of the alve ring to remain constant in position whereas the dehisced portion will give a double exposure effect Cinefluoroscopy is particularly useful when evaluating prosthetic valve function of radiopaque poppets A poppet stuck in an open position can easily be seen Abnormal motion of the prosthetic valve ring can also be observed since the normal variations in tilt of the aortic and mitral prosthetic rings is about 0 to 10 degrees during the cardiac cycle Also crack ing or grooving of the prosthetic valves may be detected

Echocardiography The use of echocardiog raphy to evaluate prosthetic valve function is gaining in popularity With echocardiography it is possible to examine the structure of the valve ring struts or cage and the motion of excursion (opening velocity closing velocity amplitude of excursion) of the poppet or disc Serial recordings are of extreme value in deciding whether or not significant changes have occurred with time As always, correlation of echocardiographic findings with the clinical data is mandatory to arrive at clinical conclusions

Long term follow up and complications

It should be anticipated that patients with severe valvular heart disease will improve mark edly following successful replacement of the diseased cardiac valve provided there is no progression of myocardial disease and if no complications related to the valve prosthesis itself arise Long term patient survival following mitral valve replacement will depend on the type of prosthesis used preoperative cardiac state (degree of cardiomyopathy functional class cardiac rhythm) the surgeon performing the operation and the ancillary personnel and facilities avail able to support the surgical procedure A 5 year survival of over 70 per cent is possible for some patients The survival rate of patients with aortic valve replacement may be slightly higher than that of patients with mitral prostheses Consid ering the operative mortality rate patients undergoing mitral valve replacement have ap proximately a 50 per cent chance of being alive at the end of 5 years whereas patients with aortic valve replacement have approximately a 30 to 40 per cent chance The outcome of a contemplated aortic or mitral valve replacement is complex and is related to the degree of associated cardiomyop athy state of coronary circulation family and social affairs ability to tolerate medications and other innumerable factors Merely successfully replacing the valve surgically does not complete the care of the patient or cure him of heart disease

Persistent severe or recurrent congestive heart failure No improvement worsening or initial improvement with later worsening of the symptoms of congestive heart failure or arrhyth mias following cardiac valve replacement should cause the physician to suspect that a problem exists in the mechanical function of the valve prosthesis A sudden catastrophic change in the patient s cardiac state should suggest valvular dysfunction

Mechanical problems *Mitral valve prostheses* may have severe periprosthetic leaks which seem to be more common when the mitral valve and mitral valve annulus are severely calcified pre *operatively* The cause of the periprosthetic leak is usually suture disruption with resultant improper anchoring of the prosthetic valve ring

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...ly who undergoes surgery for implantation of a ...ve prosthesis will usually show failure of the ...tient to improve markedly following surgery ...e history and physical examination will ...pport the lack of improvement of cardiac func...n even though significant murmurs or abnor...al prosthetic valve sounds are absent (the latter ...s useful only in a negative sense). When this ...curs, cardiomyopathy should be considered ...riously.

Occasionally, instances of cardiomyopathy and ...ongestive heart failure are related to endocardial ...brosis in the left ventricle following initial valve ...placement.[3] We have recorded electrocardio...graphic changes of ischemia in the region of the ...apillary muscles following mitral valve replace...ment. Endocardial ischemia and trauma could ...e the cause of this entity.

Thromboembolism. Despite continuing im...provement in the design of prosthetic valves and ...attempts to control the coagulation process, ...thromboembolic phenomena continue to plague ...patients and their physicians. The incidence of ...embolism may be 18 to 53 per cent among patients with mitral valve prostheses and approx...imately 25 per cent among patients with aortic valve prostheses.[2]

Despite hopes that some of the newer valve designs would eliminate the need for continued anticoagulant therapy, all patients with cardiac valve prostheses should receive anticoagulation therapy including one of the coumarin type drugs (sodium warfarin) unless a serious contraindication exists. The use of aspirin, dipyridamole, and other "antiplatelet drugs" should also be considered but never relied upon.

A high index of suspicion is always necessary to diagnose accurately the presence of cardiac thrombi in patients with prosthetic valves, especially since many thrombi do not interfere with the mechanical function of the prosthetic valve. Transient cerebral symptoms must be given proper consideration. It should be realized that emboli to many other parts of the body may be asymptomatic and may therefore go undetected. Changes in valve sounds or development of a cardiac murmur should increase suspicion of a thrombus in a patient with a valve prosthesis. Finally, when thrombi are suspected, patients should be carefully questioned concerning their reliability in taking anticoagulants as well as to their intake of other medications, e.g., foodstuffs and drugs, that might interfere with proper anticoagulation therapy.

Other embolic phenomena. Emboli may result from fragmentation of silicone poppets, from Teflon material which covers the valve struts,[11] or from infected material (vegetations) around the valve. If an embolectomy is performed, the embolus should always be examined by the pathologist, bacteriologist, and virologist. This may provide an important clue as to its origin and the nature of the therapeutic problems to follow.

Infection of valve prostheses. Although late bacterial infection of cardiac valve prostheses has been reduced to a level of 1 per cent, infection is still a hazard. Such infections can occur with little if any change in mechanical function of a prosthetic valve. Thus, fever, anemia, systemic embolism, and positive blood cultures remain the mainstays for the diagnosis of infections of the prosthetic valve. Many patients require removal of the infected prosthesis in addition to antibiotic therapy in order to eradicate the infection completely. However, therapy with large doses of appropriate antibiotics may suffice to remove the infection.

Hemolytic anemia. Intravascular hemolysis, which occurs in some patients following insertion of a valve prosthesis, may be related to mechanical dysfunction of the valve, e.g., periprosthetic leaks, thrombosis, or failure of endothelialization of the prosthesis. However, anemia occasionally occurs in the presence of a "normal" prosthetic valve. The etiology of the hemolysis in either case is presumed to be mechanical trauma to the red blood cells and probably occurs to some degree in all patients following insertion of an aortic or mitral valve prosthesis. This factor may not be the only one, however.

Generalized symptoms of anemia, e.g., weakness, lassitude, and pallor, and onset of symptoms of congestive heart failure should cause the physician to consider hemolytic anemia in patients with valve prostheses. The syndrome is recognized by the presence of anemia, low serum iron, decreased haptoglobin, marked increase in serum lactic dehydrogenase, and typical deformed and fragmented red blood cells (schistocytes) noted in the peripheral blood smear.

Other problems. Other problems associated with cardiac valve replacement are highly individual. For example, the emotional aspect asso...

Signs and symptoms of left ventricular congestive heart failure may be prominent when a significant leak is present The presence of a hemolytic anemia (see below) should also arouse suspicion of systolic or regurgitant leak Although a loud murmur of mitral insufficiency may be present, frequently little or no murmur can be heard [9] Shortening of the S OC interval and absence of the opening sound of the mitral valve prosthesis may be associated with periprosthetic systolic leaks [9, 1] The degree of shortening of the S_2 OC interval is really a crude guide to the severity of the leak The magnitude of the hemodynamic disturbance is easily determined by the clinical data If detachment of the mitral prosthetic valve exists, then chest x rays or fluoroscopy may reveal abnormal changes in position of the prosthetic valve ring during the cardiac cycle (see above) [11]

Intravalvular leak of a mitral valve prosthesis may be associated with the findings of mitral regurgitation as discussed above Such intravalvular leaks are secondary to interference with proper valve function by thrombi or fibrous growth (pannus formation) Rarely ball variance occurs in patients with ball in cage valves with silicone poppets (see below) In association with mitral regurgitation there may be hemodynamically significant mitral stenosis In either event the patient will exhibit symptoms and signs of congestive heart failure thromboembolism (see below) or both In such instances a decreased intensity and/or a delay in the onset of the opening sound of the prosthesis may occur

Echocardiography may show systolic expansion of the left atrium associated with mitral regurgitation as well as abnormalities of the opening and closing velocities of the poppet Improper contact of the poppet or disc with the valve struts might be demonstrated

Echocardiography may provide evidence for the presence of pannus formation and/or thrombosis of the prosthetic valve [1] The echocardiogram will show delayed motion of the movable part of the valve prosthesis as well as the prosthetic cage

Mechanical dysfunction of an *aortic valve prosthesis* is likely to be related to periprosthetic leaks due to disruption of sutures, to thrombosis or to ball variance This last factor is peculiar to protheses with silicone poppets, presumably due to lipid absorption and other physical and chemical changes of the poppet followed by swel[ling] sticking, fracture, distortion, or embolizatio[n of] the ball [2] Murmurs of aortic insufficiency [are] heard frequently following insertion of an ao[rtic] valve prosthesis [23] The clinician must become [well] acquainted with these murmurs so that he [can] distinguish the significant ones from those a[lso] associated with an artificial valve The [se] murmurs do not increase in intensity over sev[eral] months postoperatively and are not associa[ted] with physical signs of aortic insufficiency [As] mentioned above, certain prosthetic valves (S[mith]overn, Wada Cutter, and Bjork Shiley) are i[nher]ently incompetent making interpretation [of] diastolic murmur difficult at times

When mechanical dysfunction of an a[ortic] valve prosthesis is due to thrombus form[ation] which interferes with opening and closing o[f the] poppet or disc a diastolic murmur may be[come] apparent and a softening or muffling of [the] opening sound may occur The sudden on[set of] congestive heart failure and/or syncope [may] result from the valve poppet sticking op[en or] closed (transiently) [4] secondary to ball var[iance] or to fibrin formation on the valve struts

Cardiomyopathy may also be a cause of pe[rsist]ent congestive heart failure following satisfa[ctory] cardiac valve replacement This may be one [of the] most difficult conditions for the physici[an to] recognize in a patient with a valve pro[sthesis] Nevertheless severe cardiomyopathy occ[asion]ally irreversible may be present prior to su[rgery] to such an extent that correction of the [valve] lesion will not produce the desired ben[eficial] effect It is often considered that severe c[ardio]myopathy occurring in patients with va[lvular] heart disease is due to an inordinately long [delay] before operative intervention However, it s[hould] be remembered that virtually anything t[hat is] capable of damaging a heart valve may [also] damage the myocardium and the cardio[myo]pathic process can continue for many years

If cardiomyopathy is considered to be the [cause] of persistent congestive heart failure in a p[atient] with a cardiac valve prosthesis a serious [effort] must be undertaken to rule out problems [asso]ciated with the valve prosthesis as well as [other] medical problems e g improper digitaliz[ation,] cardiac causalgia recurrent pulmonary em[boli,] electrolyte imbalance, infection anemia, [or] other disease states A careful review o[f the] history of the patient with severe cardiom[yopathy]

Sticking aortic valve A complication of fabric-covered ball valve prosthesis J Thorac Cardiovasc Surg 63 915 1972

Najmi M and Segal B L. Auscultatory and phonocardiographic findings in patients with prosthetic ball valves Am J Cardiol. 16 794 1965

Tavel M E Clinical phonocardiography and external pulse recording Chicago 1972 Year Book Medical Publishers Inc

Lanning A M Unusual radiologic sign of loose mitral valve prosthesis *Radiology 88 89 1967*

Resnicoff S A and DeWeese J A Acute aortic insufficiency due to ball impaction in a "close clearance" Starr Edwards aortic prosthesis, Ann Thorac Surg. 11 660 1971

Bjork V O A new central flow tilting disc valve prosthesis One year's clinical experience with 103 patients J Thorac Cardiovasc Surg 60 355 1970

Gimenez J L Soulen R L and Davila J C Prosthetic valve detachment its roentgenographic recognition Am. J Roentgenol. Radium Ther Nucl Med. 103 595 1968

Johnson M L. Paton B C and Holmes J H Ultrasonic evaluation of prosthetic valve motion Circulation 41 and 42(Suppl. II) 3 1970

Mahringer W and Hausen W J Ultrasound cardiogram in patients with mitral valve disc prostheses Angiology 21 336 1970

Pfeifer J Goldschlager N Sweatman T Gerbode F and Selzer A. *Malfunction of mitral ball valve prosthesis* due to thrombus Report of 2 cases with notes on early clinical diagnosis Am J Cardiol 29 95 1972

Winters W L Jr Gimenez, J and Soloff L A Clinical application of ultrasound in the analysis of prosthetic ball valve function Am J Cardiol 19 97 1967

Duvoisin G E Wallace R B Ellis, F H Jr Anderson M W and McGoon D C Late results of cardiac valve replacement Circulation 37 and 38(Suppl II) 5 1968

Leachman R D and Cokkinos D V P Absence of opening click in dehiscence of mitral valve prostheses, N Engl J Med 281 461 1969

1 Willerson J T Kastor J A Dinsmore R E Mundth E Buckley M J Austen W G and Sanders, C A Noninvasive assessment of prosthetic mitral paravalvular and intravalvular *regurgitation* Br Heart J 34 561 1972

22. Hylen J C, Kloster F E., Starr A., and Griswold H E. Aortic ball variance diagnosis and treatment, Ann Intern Med 72 1 1970

23 Duvoisin G E and McGoon D C The advantages and disadvantages of prosthetic valves for aortic valve replacement Prog Cardiovasc Dis. 11 294 1969

24 Cokkinos, D V Vorids, E Bakoulas, G Theodossiou A and Skalkeas G D Thrombosis of two high flow prosthetic valves, J Thorac Cardiovasc Surg. 62 947 1971

25 Roberts, W C and Morrow A G Late postoperative pathological findings after cardiac valve replacement Circulation 35(Suppl. I) 48 1967

26 Giles T D and Burch, G E Experimental evidence in man of the electrocardiographic manifestations of papillary muscle dysfunction Am HEART J 82 193 1971

27 Akbarian M Austen, W G Yurchak, P M., and Scannell J G Thromboembolic complications of prosthetic cardiac valves Circulation 37 826 1968

28 Levine F H Copeland J G and Morrow A G Prosthetic replacement of the mitral valve Continuing assessments of the 100 patients operated upon during 1961 1965 Circulation 47 518 1973

29 Sullivan J M Harken, D E and Gorlin R Pharmacologic control of thromboembolic complications of cardiac valve replacement N Engl. J Med. 284 1391 1971

30 Weily H S and Genton E Altered platelet function in patients with prosthetic mitral valves Circulation 42 967 1970

31 Niles N R Teflon embolism from Starr Edwards valves, J Thorac Cardiovasc Surg. 59 94 1970

32 Block P C DeSanctis R W Weinberg, A. N., and Austen W G Prosthetic valve endocarditis, J Thorac Cardiovasc Surg 60 540 1970

33 Indeglia R A Shea M A Varco R L. and Bernstein E F Erythrocyte destruction by prosthetic heart valves Circulation 37 and 38(Suppl. 2) 86 1968

34 Burch G E and Giles, T D Cardiac causalgia, Arch. Intern Med 125 809 1970

ciated with cardiac valve prostheses especially when the valve sounds are audible to the patient, may be cause for concern Control of anticoagulant therapy will depend to a large degree on patient reliability, hepatic status, and reaction of the patient to continued medication The postpericardiotomy syndrome (cardiac causalgia) may also complicate the postoperative course of patients with cardiac valve replacement

Far too often after prosthetic valve insertion patients feel that they are or should be cured and are not properly impressed with the need for meticulous medical therapy It is a rare patient indeed, who does not have residual cardiomyopathy following valve replacement Moreover patients realize that their lives are dependent on a mechanical manmade object This fact disturbs many patients

The postpericardiotomy syndrome may be particularly bothersome to some patients This may take the form of cardiac causalgia [11] and the intermittent left chest and arm discomfort may cause the patient to feel that his heart is getting worse Reassurance by the physician is of paramount importance in preventing the patient from developing a serious neurosis or addiction to pain relieving drugs

Finally the insertion of a cardiac valve prosthesis does not protect the patient from other diseases of the heart Thus careful management of the patient with a valve prosthesis includes close observation for the development of vascular disease as well as disease of the endocardium myocardium and pericardium

There is no doubt that prosthetic valves not only can be life saving but can improve hemodynamic cardiac and circulatory function when they are satisfactorily inserted All hemodynamic studies along with clinical data attest to these conclusions Unfortunately however complications are common and only a relatively few last a long time without disturbances in function These are foreign bodies and it is well known how the body reacts to foreign bodies Because these valves fail to last long periods of time in most instances it is the responsibility of the cardiologist to make sure a prosthetic valve is really needed The patient s own valve even though it is scarred, is his own tissue and will last many years and can function sufficiently well even though it is clinically or acutely diseased Thus mitral commissurotomy is indicated in preference to mitral valve replacement in most patients Wh the commissurotomy is done well, the result c be excellent for many years with only m complications Good medical care of patients w scarred valves can result in acceptable card function for many years

Summary

The clinical follow up for a large number of patients with aortic and mitral valve prostheses is now the responsibility of the general internist a cardiologist particularly those physicians wh recommended operation Proper follow up patients with prosthetic heart valves can b performed only if the physician is aware of th natural history of the patient following valv replacement as well as of the common complica tions associated with cardiac valve prostheses

This article discusses the hemodynamic changes which follow cardiac valve replacement complications associated with valve replacement (congestive heart failure suture disruption ba variance thromboembolism hemolysis, cardio myopathy etc) and simple clinical means of detecting these complications Some special tech niques which may be useful in diagnosing compli cations of prosthetic cardiac valve malfunctio are described It is emphasized that the physician should not consider the patient cured once he has undergone cardiac valve replacement b t rather should consider him to be the subject of meticulous long term medical care

REFERENCES

1 Pluth J R and McGoon D C Current status of h ar valve replacement Mod Concepts Cardiovasc Di 43 65 1974
2 Carey J S and Plested W G Immediate hemody namic response to correction of cardiac valvular les rs Ann Thorac Surg 13 311 1972
3 Hawe A Frye R L and Ellis F H Jr Late hemody namic studies after mitral valve surgery J Thor Cardiovasc Surg 65 351 1973
4 Morgan J J Hemodynamics one year following mitr valve replacement Am J Cardiol 19 189 1967
5 Morrow A G Clark W D Harrison D C a Braunwald E Prosthetic replacement of the mit valve Operative methods and the results of preoperati and postoperative hemodynamic assessments, Circul tion 29(Suppl) 2 1964
6 Messmer B J Okies J F Hallman G I and Cool D A Mitral valve replacement with the Bjork Shil tilting disc prosthesis J Thorac Cardiovasc Sur 62 938 1971
7 Wada J Komatsu S and Kamata K Cardiac valv replacement with Wada Cutter prosthesis Ann Thora Surg 14 38 1972.
8 Mullin M J Muth W F and McNamara J J

Sticking aortic valve A complication of fabric covered ball valve prosthesis J Thorac Cardiovasc Surg 63 ?15 19 2

Najmi M and Segal, [illegible] L. Auscultatory and phonocardiographic findings in patients with prosth tic ball valves Am J Cardiol. 16 94 1965

Tavel M [illegible] Clinical phonocardiography and external pulse recording Chicago 19,2 Year Book Medical Publishers Inc

Lansing A M *Unusual radiologic sign of loose mitral* valve prosthesis Radiology 88 89 1967

Resnicoff S A and DeWeese J A Acute aortic insufficiency due to ball impaction in a "close clearance" Starr Edwards aortic prosthesis, Ann Thorac Surg 12 660 1971

Bjork V O A new central flow tilting disc valve prosthesis One year's clinical experience with 103 patients J Thorac *Cardiovasc* Surg 60 3o5 19 0

Gimenez J L Soulen R L and Davila J C Prosthetic valve detachment its roentgenographic recognition Am J Roentgenol Radium Ther Nucl Med 103 o9 1968

Johnson M L Paton [illegible] C and Holmes J H Ultrasonic evaluation of prosthetic valve motion Circulation 41 and 42(Suppl. II) 3 19 0

Mahrin er W and Hausen W J *Ultrasound cardiogram* in patients with mitral valve *disc* pro theses, Angiology 21 336 19 0

Pf ifer J Goldschlager N Sweatman T Gerbode F and Selzer A Malfunction of mitral ball valve prosthesis due to thrombus Report of ? cases with notes on early clinical diagnosis, Am J Cardiol 29 95 19,2

Winters, W L Jr Gimenez J and Soloff L A Clinical application of ultrasound *in the analysis of prosthetic* ball val e function Am J Cardiol 19 97 1967

Duvoisin G E Wallace R B Ellis F H Jr Anderson [illegible] W and McGoon [illegible] C Late results of cardiac valve replacement Circulation 37 and 38(Suppl II) 5 1968

Leachman R D and Cokkinos D V P Absence of opening click in dehiscence of mitral valve prostheses N Engl J Med 281 461 1969

Willerson J T Kastor J A Dinsmore R E Mundth E Buckley M J Austen W G and Sanders C A Noninvasive assessment of prosthetic mitral paravalvular and intravalvular regurgitation Br Heart J 34 ,61 19,2.

22 Hylen J C., Kloster F E Starr A., and Griswold H E Aortic ball variance *diagnosis and treatment* Ann Intern Med 72 1 19 0

23 Duvoisin [illegible] E and McGoon D C The advantages and disadvantages of prosthetic valves for aortic valve replacement Prog. Cardiovasc Dis 11 ?94 1969

-4 Cokkinos D V Voridis, E., Bakoulas, G., Theodossiou A and Skalkeas, G D Thrombosis of two high flow prosthetic valves, J Thorac Cardiovasc Surg 62 947 1971

25 Roberts, W C and Morrow A G Late po toperative pathological findings after cardiac valve replacement Circulation 35(Suppl 1) 48 1967

-6 Giles, T D and Burch, G E Experimental evidence in *man of the electrocardiographic manifestations of papil*lary muscle dysfunction Am Heart J 82 193 1971

27 Akbarian M Austen W G Yurchak P M., and Scannell J G Thromboembolic complications of prosthetic cardiac valves, Circulation 37 8-6 1968

28 Levine F H Copeland J G and Morrow A G Pro thetic replacement of the mitral valve Continuing assessments of the 100 patients operated upon during 1961 196o *Circulation* 47 518, 19,3

29 Sullivan J M Harken D E and Corlin R. Pharmacologic control of thromboembolic complications of cardiac valve replacement N Engl. J Med 284 1391 19,1

30 Weily H S and Genton E Altered platelet function in patients with prosthetic mitral valves Circulation 42 967 1J 0

31 Niles N R *Teflon embolism from* Starr Edwards valves J Thorac Cardiovasc Surg 59 ?94 19,0

3? Block P C DeSanctis, R W Weinberg, A N., and Austen W G Prosthetic valve endocarditis, J Thorac Cardiovasc Surg 60 540 1J?0

33 Indeglia R A Shea M A Varco R L. and Bernstein E F Erythrocyte destruction by prosthetic heart valves, Circulation 37 and 38(Suppl ?) 86 1968

34 Burch G E and *Giles* T D Cardiac causalgia, Arch Intern Med 125 809 19 0

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Drugs in the management of hypertension Part III

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Vasodilator drugs

The vasodilator drugs act directly on vascular smooth muscle to produce vasodilatation and reduction in peripheral resistance They include hydralazine diazoxide minoxidil guancydine and sodium nitroprusside With the exception of sodium nitroprusside these drugs have a selective effect on arterioles with little if any effect on venous capacitance vessels This selective dilatation of arterioles results in an increase in venous return which triggers a reflex increase in heart rate and stroke volume mediated through the sympathetic nervous system As a result they share several common side effects due to increased cardiac action These include palpitation headache and the capacity to precipitate angina pectoris in patients with coronary disease In addition drugs in this group share an ability to stimulate renin release and promote sodium retention Increased cardiac output and sodium retention both act to reduce the hypotensive effects of vasodilatation In most circumstances drugs in this group should be used together with propranolol and diuretics which counteract these effects enhance the effectiveness of vasodilatation and minimize side effects

Of the vasodilators only hydralazine is available for oral use in the United States at present Minoxidil and guancydine have given promising results in clinical trials Diazoxide and sodium nitroprusside are available only for intravenous use although diazoxide has been shown to be effective given orally [3]

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Oral vasodilators

Hydralazine

Actions

Hydralazine has been in use since the earl 1950 s It acts directly on arteriolar smooth muscle producing vasodilatation and reduction in peripheral resistance Splanchnic, coronary, cerebral and renal blood flow increase while blood flow in skeletal muscle and skin is unaffected. Blood pressure is reduced in both the supine and standing posture Hydralazine is rapidly absorbed from the gastrointestinal tract, reaching maxima effect in one hour and the usual half life is fou hours However this varies among individual depending on the rate of inactivation of the dru by acetylation Slow acetylators are mor responsive to hydralazine and more likely t develop immunological side effects Hydralazin produces immediate stimulation of renin releas which through its effect on aldosterone is at lea partly responsible for sodium retention Wit long term use of hydralazine alone sodium reten tion suppresses the renin stimulation effect

Uses

Although it has been available for many yea hydralazine has until recently had limited u because of its tendency to cause increased hea rate and cardiac output When used in combin tion with a diuretic and propranolol these effec are largely eliminated and a greater hypotens effect is achieved This combination has prov effective in managing patients who previou were poorly controlled on other drug regimens A dose related hypotensive response can demonstrated up to 800 mg per day Howev long term use at high dosage produces a hi incidence of immunologic side effects and t dose should generally be kept to 300 mg per d or less

effects

ymptoms related to reflex increase in cardiac and output include palpitations headache angina pectoris Many patients develop posi antinuclear antibody reaction on prolonged and a syndrome similar to lupus erythema is disseminatus occurs in 10 to 20 per cent of ients on doses greater than 400 mg per day s occurs with much lower frequency on doses than 300 mg per day[37] Other side effects lude fever skin eruptions nausea anorexia l diarrhea Many patients complain of flush ill defined rushing sensations in the head and ntal fuzziness Peripheral neuropathy and ne marrow depression have been reported

noxidil

tions

Minoxidil is a potent vasodilating agent which not yet available for general use Like the other ugs in this group it acts directly on vascular nooth muscle selectively dilating arteriolar sistance vessels with little or no effect on nous capacitance vessels This results in creased venous return and triggers a reflex crease in heart rate and cardiac output ediated by the sympathetic nervous system his drug also promotes sodium retention by imulating renin release and probably also by a irect effect on the renal tubule Minoxidil is onsiderably more potent than either hydralazine r guancydine When used alone its effectiveness gradually lost as a result of increased cardiac utput and sodium retention When used togeth r with propranolol and a diuretic these effects re counteracted and tachyphylaxis does not levelop Minoxidil is rapidly and completely absorbed from the gastrointestinal tract with eak plasma levels in 1 hour and a plasma half ife of 4 hours The hypotensive effect does not orrespond to the plasma concentration This is due to accumulation of the drug in arterial smooth muscle where it exerts an effect which is prolonged for 12 hours or more After stopping the drug blood pressure does not rise for several days although over 90 per cent of the drug and its metabolites are excreted in 24 to 48 hours[88] Minoxidil lowers blood pressure in both the supine and standing posture and does not affect renal blood flow or glomerular filtration rate

Uses

Minoxidil appears to be an extremely promising drug for clinical use In clinical trials it has been shown to be remarkably effective in controlling blood pressure in patients with severe and refrac tory hypertension and renal failure who have failed to respond to any of the drug regimens now available[90, 91] Furthermore when used in combi nation with propranolol and diuretics it has produced no serious side effects in human subjects The sodium retaining effect of minoxidil does not seem to be correlated with renin and aldosterone levels In patients with renal failure good blood pressure control has required meticu lous adjustment of diuretic agents to control fluid retention and of propranolol to control reflex cardiac stimulation Pettinger and Mitchell[1] report a useful additive effect when several different types of diuretics were used together in patients on minoxidil Doses of 2 to 40 mg per day have been well tolerated in man Patients formerly incapacitated by hypertension and renal failure have tolerated minoxidil propranolol and diuretic therapy with few drug side effects unim paired sexual function and improvement in cardiac status The long duration of action of minoxidil allows simple dosage schedules

Side effects

After prolonged use at high dose levels in dogs a myocytic degenerative lesion of the right atrium frequently develops Although this has not been reported in other species this finding may account for the delay in releasing minoxidil for general use In man minoxidil has been free of serious side effects and has not caused the lupus like syndrome seen with hydralazine In doses of 10 mg per day and more minoxidil regularly produces hirsutism which is most marked in the first few months and then tends to recede some what[91] Characteristically the temporal hair line grows toward the eyebrows and there is increase in upper truncal hair in males and increased lanugo hair in females[4] The mechanism is unknown but similar hirsutism occurs in patients on oral diazoxide[5] No change in gonadal or adrenal function has been found Minoxidil has been shown to stimulate hair growth when applied directly to the skin[4] Hirsutism is easily controlled with depilatory procedures

Guancydine

Actions

Although it is not yet available for general use guancydine has been used in clinical trials since

1968 Its mode of action is similar to the other vasodilating drugs It acts directly on arteriolar smooth muscle causing vasodilatation and decreasing peripheral resistance It has little if any effect on venous capacitance vessels Thus it increases venous return, and like the other drugs in this group, it stimulates reflex increase in cardiac output and heart rate stimulates renin release in some but not all patients and causes sodium retention These side effects are counteracted when guancydine is used in combination with propranolol and a diuretic [11] Taken orally guancydine is well absorbed from the gastrointestinal tract and produces a hypotensive effect which is maximal in 1 1/2 hours and lasts four to eight hours It is effective in both the supine and standing posture In potency it is equal to or somewhat greater than hydralazine

Uses

Guancydine shows promise as a vasodilator to be used in combination with diuretic and beta adrenergic blocking agents to offset the cardiac stimulation and sodium retention which all such drugs produce It does not cause the immunologic side effects seen with hydralazine nor the right atrial lesion reported in dogs on high doses of minoxidil Its position in therapy is still uncertain It should not be used alone but shows promise as an alternative to hydralazine Doses up to 1500 mg per day have been tolerated in man Higher doses usually produce intolerable side effects

Side effects

When used in combination with propranolol and a diuretic palpitation headache chest discomfort and edema do not occur However guancydine side effects include gynecomastia galactorrhea nausea epigastric distress mental confusion and hallucinations most of which are dose related

Intravenous vasodilators

Diazoxide

After clinical studies extending over more than 10 years diazoxide has been released for intravenous use in hypertensive emergencies Diazoxide exerts its action by a direct effect on smooth muscle of arteriolar resistance vessels causing vasodilatation and decreased peripheral resistance It has little if any effect on venous capacitance vessels Thus it increases venous return and stimulates a marked reflex increase in cardiac output and heart rate It also promotes sodium retention both by stimulating the renin angiotensin system and by a direct effect on the renal tubule [14] Diazoxide also affects nonvascular smooth muscle causing transient reduction gastrointestinal motility [95] and relaxation of the uterus [6] It causes hyperglycemia partly by inhibiting release of insulin and partly by an extrapancreatic mechanism [6]

To be effective, diazoxide must be given by rapid bolus injection This is attributed to binding of the drug by plasma albumin which prevents it from reaching vascular receptor sites unless it is rapidly administered [8] This explanation has been criticized on theoretical grounds and it has also been shown that diazoxide produces a hypotensive effect when given by mouth although it is not available for oral use in the United States

Following intravenous injection blood pressure drops rapidly reaching a nadir in one to three minutes then rising slightly over five to ten minutes to a plateau which is sustained for some hours before rising to pretreatment level Blood pressure characteristically drops to a satisfactory or normal level and hypotensive reactions are uncommon Duration of the hypotensive effect is variable lasting from two to 24 hours Blood levels of the drug are poorly correlated with the hypotensive action The drug is excreted unchanged in the urine over a 30 hour period

Uses

Intravenous use of diazoxide has proved effective for short term management of acute hypertensive emergencies especially hypertensive encephalopathy Its advantages are its rapid onset of action the absence of a sedative effect and the rarity of excessive hypotension Since the drug reaches maximal effectiveness rapidly close monitoring is required for only a short time after each dose Since it causes marked reflex increase in cardiac action it should not be used in dissecting aneurysm of the aorta or in the presence of coronary insufficiency where sodium nitroprusside is preferable Although diazoxide causes abrupt cessation of labor it has been used successfully in eclampsia when used with oxytocin which overrides its relaxing effect on the uterus Diazoxide is ineffective in pheochromocytoma It should be used together with intravenous furosemide to offset its sodium retaining effect Use of propranolol with diazoxide is hazardous Although propranolol counteracts the

-ex stimulation of cardiac action use of the two gs together may result in severe hypotension less the dose of diazoxide is reduced[6] It has -n claimed that short term use of intravenous zoxide alters the course of severe hypertension king patients more responsive to subsequent of other drugs [8] Other investigators have not nfirmed this finding

Diazoxide is effective in many patients hough resistance occurs in some requiring rease in dosage or substitution by sodium troprusside During treatment with diazoxide ood sugar should be monitored frequently and al hypoglycemic agents or insulin may be re ured for blood sugar control Oral antihyperten agents should be substituted for diazoxide as on as the clinical status of the patient is able

de effects

Sodium retention with diazoxide is readily ounteracted with diuretics (preferably furose nide) given simultaneously Tachycardia occurs gularly and can precipitate angina pectoris Hyperglycemia is a frequent occurrence and yperosmolar non ketotic coma has been re orted Postural hypotension can occur with ombined diazoxide and furosemide therapy but usually corrected by keeping the patient in upine position Hypotensive reactions are likely o occur when diazoxide is used in patients ogether with propranolol Hypotension also occurs occasionally in patients on multiple anti hypertensive drugs Diazoxide can displace cou marin anticoagulants from binding proteins amplifying the effect of the anticoagulant Mild reactions of flushing and abdominal discomfort occur frequently Oral diazoxide causes hypertri chosis and extrapyramidal symptoms

Sodium nitroprusside

Actions

The effectiveness of intravenous sodium nitro prusside for rapid blood pressure reduction has been known for many years but it has become commercially available only very recently In its mode of action sodium nitroprusside differs from all the other vasodilating drugs in that it acts both on the arteriolar resistance vessel and also on the venous capacitance vessels This results in a drop in peripheral resistance without an in crease in venous return As a result it does not regularly result in a reflex increase in cardiac output and heart rate Its effect on cardiac output will vary depending on the prior state of the patient [11] and on posture Tilting the patient will produce pooling of blood in capaci tance vessels and reduce cardiac output [8 11] Sodium nitroprusside must be given by constant infusion preferably with the aid of an infusion pump It is reliably effective in almost all patients exerting its effects within seconds Its hypotensive action is dissipated within a few minutes after infusion is stopped Conversion of nitroprusside to thiocyanate occurs rapidly in vivo Thiocyanate is relatively non toxic at plasma levels below 10 mg per 100 ml Thiocya nate is excreted in the urine and may accumulate with time in patients with reduced renal func tion

Uses

Sodium nitroprusside is an extremely effective and useful drug for intravenous treatment in all types of hypertensive emergencies Because of its unique effect on both arterioles and venous smooth muscle it does not stimulate reflex increase in cardiac action For this reason it is the drug of choice for treatment of hypertension associated with dissecting aneurysm of the aorta congestive heart failure and myocardial infarc tion It has recently seen increasing use in reducing ventricular afterload in patients with myocardial infarction

Sodium nitroprusside is ineffective if given by mouth Rate of intravenous infusion must be very carefully regulated preferably by an infusion pump Blood pressure must be monitored con stantly and an indwelling arterial cannula is usually necessary for this purpose Serum levels of thiocyanate can be by methods easily performed in most clinical laboratories Thio cyanate should be monitored in patients receiving sodium nitroprusside for more than 24 or 48 hours and in those with renal insufficiency and should be kept below 10 mg per 100 ml The drug is light sensitive It must be made fresh every 24 hours and administered from a dark or foil wrapped bottle Oral antihypertensive agents should be substituted for sodium nitroprusside as rapidly as the clinical status of the patient allows it

Side effects

Toxicity of sodium nitroprusside is usually mild at therapeutic dose levels and at blood levels below 10 mg per 100 ml However nausea dizzi ness agitation muscle spasms chills nasal stuffi ness confusion and toxic psychosis can occur

and are generally dose related The drug can regularly produce profound hypotension if the rate of infusion is increased At toxic levels tremors and sudden respiratory arrest can occur

Beta adrenergic blocking agents

Actions

The beta adrenergic blocking agents, of which propranolol is still the only member currently available in the United States have been used clinically since 1964 as antihypertensive agents

The earliest reports on the antihypertensive action of beta adrenergic blockade suggested that the reduction in blood pressure was due to a primary reduction in cardiac output resulting from the negative inotropic and chronotropic action of these drugs [10] [118] There is evidence both in man and in animals that sympathetic stimulation promotes release of renin in the kidney and that propranolol inhibits renin release [1] [11] Buhler and associates[6] reported that propranolol was more likely to produce a fall in blood pressure in patients with high plasma renin activity than in patients with normal or low plasma renin activity Other investigators have not confirmed Buhler s work [111]

Another important mechanism of action of propranolol in the treatment of hypertension is its ability to prevent reflex stimulation of the heart rate and cardiac output resulting from the primary action of vasodilating agents such as hydralazine When used alone the effectiveness of vasodilating agents is limited by a reflex increase in sympathetic discharge triggered by peripheral vasodilatation Propranolol blocks these effects and facilitates the vasodilating effect of these agents A combination of propranolol in a dose of 80 to 160 mg per day and hydralazine in a dose of 100 to 400 mg per day resulted in satisfactory blood pressure control in a group of patients not previously controlled with other drug programs [10]

Another mechanism of action of propranolol may be a direct effect on the central nervous system (brain stem) resulting in a decrease in the sympathetic tone [11] This action probably only occurs with doses of propranolol exceeding 160 mg per day

Uses

Patients with hypertension who also clinically exhibit a hyperdynamic circulatory state are ideal candidates for beta blockade therapy Such patients have a disturbing cardiac awareness manifested by an unpleasant rapid and forceful cardiac action [113] Gorlin[114] has reported hemodynamic studies on these patients and describes them as having a hyperkinetic heart syndrome Propranolol therapy for hypertension in this group seems to work well [115]

In all patients with hypertension propranolol may produce a smooth lowering of systolic and diastolic blood pressure without postural hypotension A number of trials demonstrate that when the drug is used in a sufficient dose the antihypertensive effect is substantial and comparable to that produced by methyldopa and guanethidine [11] [11] Other workers report that the drug produces only a modest and at times inconsequential reduction in blood pressure [113] [11]

At present propranolol shows greatest promise as an agent to use in combination with the vasodilators The cardiac effects of the two drugs oppose each other vasodilators increasing and propranolol decreasing both heart rate and cardiac output The modifying effect of propranolol thus allows the full vasodilatory effect of these drugs to be exerted Balanced against each other the side effects of each drug tend to be cancelled by the action of the other drug

The use of propranolol together with guanethidine demands caution since both drugs depress myocardial contractility and heart rate Data concerning the effects of using propranolol together with other antihypertensive agents are scanty

The effective dose of propranolol varies widely among patients The initial amount should be approximately 40 to 60 mg per day in divided doses and should not be increased more often than once every two to three days to avoid cumulative pharmacologic effects The dose can be increased until a desired effect is achieved unless heart rate slows to less than 50 per minute Doses up to 1 000 mg per day have been used in the treatment of hypertension Other beta adrenergic blocking drugs that may be more cardioselective in action are currently being studied

In using propranolol in combination with hydralazine it is best to start both drugs simultaneously beginning with 50 to 75 mg per day of hydralazine and 40 to 60 mg per day of propranolol in divided doses Dosage may then be increased gradually until satisfactory blood pressure control is achieved It i [illegible] eferable to kee

ses of each drug below 300 mg per day al ough larger doses have been used One of the al diuretic agents is usually also used with this mbination

It has been reported[6] that the patients with gh plasma renin levels respond better to propra olol than those with low or normal plasma nin

de effects

Propranolol is relatively free of side effects if rtain precautions are observed Because the eta blocking drugs diminish myocardial contrac lity they should not ordinarily be used in atients with cardiomegaly or a history of ongestive heart failure Propranolol treatment hould not in general be initiated in patients with radycardia The dose should be reduced if the inus rate falls to less than 50 per minute during reatment Because beta adrenergic blockade nay potentiate atrioventricular block the drug hould not be used in patients with atrioventric ular conduction defects Propranolol may pro duce or aggravate bronchospasm in patients with a history of asthma or chronic obstructive lung disease Other side effects are minimal and consist of occasional nausea diarrhea cramps and fa tigue The fatigue in occasional patients may be quite disabling and necessitate reduction in dose or discontinuing the drug

Ganglionic blocking agents

Actions

The ganglionic blocking drugs reduce blood pressure by interfering with neurotransmission in the sympathetic ganglions These drugs compete with *acetylcholine for cholinoceptive sites in the* ganglion and thereby prevent postsynaptic depo larization The interference with transmission in sympathetic ganglions produced by these drugs results in a decreased sympathetic tone causing a decrease in peripheral vascular resistance and a fall in blood pressure The ganglionic blockers reduce cardiac output by decreasing venous return to the heart rather than by any direct action on the myocardium Peripheral pooling of blood as a consequence of venous dilatation accounts for the decrease in venous return

Changes in the heart rate are not predictable and depend upon the degree of impairment of vagal tone due to parasympathetic ganglionic blockade Almost invariably renal blood flow and glomer ular filtration rate are reduced by these drugs

Uses

The only commonly used ganglionic blocking drug at present is trimethaphan camsylate (Arfonad) which is used intravenously for the purpose of emergency reduction in blood pressure Trimethaphan has all the pharmacologic effects of the longer acting oral *drugs but has a very brief* duration of action Tolerance to trimethaphan develops rapidly and many patients become refractory to its effects in 48 to 72 hours A significant hypotensive *effect* is evident within minutes after starting an intravenous infusion of trimethaphan This drug is particularly useful in immediately lowering blood pressure in patients with acute dissection of the aorta because it reduces cardiac output together with blood pres sure Intravenous nitroprusside (not a ganglionic blocker) is also ideal in this situation whereas diazoxide is contraindicated in the treatment of dissection of the aorta because it elicits reflex increase in cardiac output Trimethaphan also may be used for the emergency lowering of blood pressure in patients with hypertensive encepha lopathy and malignant hypertension although diazoxide and nitroprusside are equally satisfac tory agents for these disorders Other hypotensive agents should be started on the first day of treatment with trimethaphan in order that blood pressure will be adequately controlled when patients become refractory to the drug Slanting of the bed in the head up position augments the hypotensive effect of trimethaphan as the drug effect is primarily an orthostatic one

Side effects

There are numerous side effects of the *ganglionic blocking agents resulting from their* widespread actions on the autonomic nervous system Parasympathetic blockade produces many disturbing symptoms including drying of the mucous membranes and paralysis of ac commodation Generalized ganglionic blockade usually results in constipation paralytic ileus urinary retention and impotence in males Postural hypotension is a common problem due to the peripheral pooling of blood The side effects are dose related and respond to reduction in dosage or omission of the drug

Selection of antihypertensive drugs

For virtually all patients with hypertension treatment with a diuretic agent should be a first choice Diuretic therapy alone is adequate to control blood pressure in many patients with mild

to moderate hypertension, and is generally smooth in its effect and relatively free of serious side effects If diuretic therapy fails to control blood pressure additional drugs may be added but diuretic therapy should be continued since an additive hypotensive effect is thereby achieved Furthermore the antiadrenergic and vasodilator drugs promote sodium retention and this is counteracted by the diuretic

It has been suggested that propranolol alone may be the drug of choice in patients with high renin and that vigorous diuretic therapy is especially effective in patients with low renin hypertension A more balanced view is presented by Koch Weser

Drug therapy with several agents simultaneously is necessary in most patients with more than mild blood pressure elevation Many patients respond well to combinations of a diuretic and an antiadrenergic medication preferably methyldopa Others including many patients with accelerated or malignant hypertension respond better to combinations of a diuretic propranolol and hydralazine For patients with severe hypertension who do not respond satisfactorily to either regimen substitution of hydralazine by minoxidil or guancydine may offer hope of more satisfactory control when these agents are released for general use Meanwhile combinations of all available types of antihypertensive agents are occasionally required in those patients with the most severe and resistant forms of hypertension The role of clonidine in therapy is still not clear At present it seems most useful as an alternative to methyldopa in patients who tolerate this drug poorly

Since treatment of hypertension is primarily designed to reduce the risk of cardiovascular disease drug therapy should be supplemented by attention to other coexistent cardiovascular risk factors such as obesity hyperlipidemia cigarette smoking and physical conditioning

REFERENCES

79 Becker Christensen F Burg H O and Ditzel J Treatment of severe hypertension with Catapres (St 155) Acta Med Scand **190** 21 1971

80 Lutzeys M R and Hoobler W W Comparison of clonidine and methyldopa on blood pressure and side effects in hypertensive patients AM HEART J **83** 464 1972

81 Mroczek W J Leibel B A and Finnerty F A Comparison of clonidine and methyldopa in hypertensive patients receiving a diuretic Am J Cardiol **29** 712 1972

82 Hunyor S N Hansson L Harrison T S and Hoobler S W Effects of clonidine withdrawal Possible mechanisms and suggestions for management Br Med J **2** 209 1973

83 Pohl J E F and Thurston H Use of diazoxide in hypertension with renal failure Br Med J 4 1971

84 Ablad B A study of the mechanism of the hemodynamic effects of hydralazine in man Acta Pharmacol Toxicol **20** (Suppl 1) 1 53 1963

85 Koch Weser J Vasodilator drugs in the treatment of hypertension Arch Intern Med **133** 1017 1974

86 Perry H M Jr Tan M Carmody S and Sakai A Relationship of acetyl transferase activity antinuclear antibodies and toxic symptoms in hypertensive patients treated with hydralazine J Lab Clin Med **76** 114 1970

87 Zacest R Gilmore E and Koch Weser J Treatment of essential hypertension with combined vasodilation and beta adrenergic blockade N Engl J Med **286** 617 1972

88 Chidsey C A Gottlieb T B Pluss R G Orr J C and Weil J V The use of vasodilator and beta adrenergic blockade in hypertension *in* Hypertension mechanisms and management edited by G Onesti K E Kim and J H Moyer New York 1973 Grune & Stratton Inc pp 357 367

89 Chidsey C A and Gottlieb T B The pharmacologic basis of antihypertensive therapy The role of vasodilator drugs Progr Cardiovasc Dis **17** [illegible] 1974

90 Gottlieb T B Katz F H and Chidsey C A Combined therapy with vasodilator drugs and beta adrenergic blockade in hypertension—A comparative study of minoxidil and hydralazine Circulation **45** 571 1972

91 Pettinger W A and Mitchell H C Minoxidil—A alternative to nephrectomy in refractory hypertension N Engl J Med **167** 171 1973

92 Hammer J Ulrych M and Freis E D Hemodynamic and therapeutic effects of guancydine in hypertension Clin Pharmacol Ther **12** 78 1971

93 Gupta N and Goldberg L I Guancydine a new vasodilator Comparison with hydralazine in a regimen including propranolol and quinethazone *in* Hypertension Mechanism and management edited by G Onesti K Kim and J Moyer New York 1973 Grune & Stratton Inc pp 361 366

94 Johnson B F Diazoxide and renal function in man Clin Pharmacol Ther **12** 815 1971

95 Beamer V L and McDonald R H Failure of repeated diazoxide injections to modify the course of severe hypertension AM HEART J **79** 749 1970

96 Landesman R Coutinho E M Wilson K H and Lopez A C V The relaxant effect of diazoxide on nongravid human myometrium in vivo Am J Obstet Gynecol **102** 1080 1968

97 Fajans S S Floyd J C Jr Thiffault C A Knopf R F Harrison T S and Conn J W Further studies on diazoxide suppression of insulin release from abnormal and normal islet tissue in man Ann N Y Acad Sci **150** 261 1968

98 Sellers E M and Koch Weser J Protein binding and vascular activity of diazoxide N Engl J Med **281** 1141 1969

99 Miller W E Gifford R W Humphrey D C and Vidt D G Management of severe hypertension with intravenous injections of diazoxide Am J Cardiol **24** 870 1969

100 Finnerty F A Jr ...

The lon term effect of repeated acute reductions of arterial pressure with diazoxide in patients with severe hypertension Ann N Y Acad Sci 150 461 1968

1 Sellers, [redacted] M and Koch Weser J Displacement of warfarin from human albumin by diazoxide and ethacrynic mefanamic and nalidixic acid Clin Pharmacol. Ther 11 524 1970

2 Thurston H and Pohl J [redacted] F Development of extrapyramidal symptoms in hypertensive patients treated with diazoxide Br Med J 3 4 4 13 3

03 Palmer F R and Lasseter K C Drug therapy Sodium nitroprusside N Engl J Med 292 294 19 5

04 Franciosa J A Giulha N H and Limas C J Improved left ventricular function during nitroprusside infusion in acute myocardial infarction Lancet 1 650 19 2

05 Tuzel I Limjuco R and Kahn D Sodium nitroprusside in hypertensive emergencies Curr Ther Res 17 95 19 5

06 Barker M H The blood cyanates in the treatment of hypertension J.A.M.A 106 67 1936

07 Frohlich E D Tarazi R C Dustan H P and Page I H The paradox of beta adrenergic blockade in hypertension Circulation 37 417 1968

108 Wilson D F Watson O F Peel J S Langley R B and Turner A S Some hemodynamic effects of trasicor (Ciba 39089/Ba) N Zealand J M 68 145 1968

109 Winer N Chokshi D S Yoon M S and Freedman A D Adrenergic receptor mediation of renin secretion J Clin Endocrinol Metab 29 1168 1969

110 Michelakis A M and McAllister R G The effect of chronic adrenergic receptor blockade on plasma renin activity in man J Clin Endocrinol Metab 34 386 19 2

111 Tarazi R C Long term hemodynamic effects of beta adrenergic blockade in hypertension in Hypertension Mechanism and management edited by G Onesti K Kim and J Moyer New York 19 3 Grune & Stratton Inc p 347

112 Stern S Hoffman M., and Braun K Cardiovascular responses to carotid and vertebral artery infusions of propranolol. Cardiovasc Res. 5 425 1971

113 Frohlich [redacted] D Dustan H P and Page I H Hyperdynamic beta adrenergic circulatory state Arch. Intern Med 117 614 1966.

114 Gorlin R The hyperkinetic heart syndrome J.A M A 182 823 1962

115 Frohlich E D The use of beta adrenergic blockade in hypertension in Hypertension Mechanisms and management edited by G Onesti K Kim and J Moyer New York 1973 Grune & Stratton Inc pp 335-336

116 Prichard [redacted] N C Propranolol as an antihypertensive agent AM HEART J 79 128 19 0

117 Prichard B [redacted] C., and Gillam, P M [redacted] Propranolol in hypertension Am J Cardiol 18 387 1966

118 Waal, H J Hypotensive action of propranolol Clin Pharmacol. Ther 7 568 1966

119 Humphreys, [redacted] S., and Delvin D [redacted] Ineffectiveness of propranolol in hypertensive Jamaicans Br Med J 2 601 1968

120 Wilson A G Brooke O G Lloyd [redacted] J and Robinson, [redacted] F Mechanism of action of β adrenergic receptor blocking agents in angina pectoris Comparison of action of propranolol with dexpropranolol and practolol. Br Med J 4 399 1969

121 Volle R. L and Koelle G B Ganglionic stimulating and blocking agents, in The pharmacological basis of therapeutics fourth edition edited by L. [redacted] Goodman and A. Gilman New York, 19 0 Macmillan Publishing Company Inc pp 585-600

122 Ford R V Moyer J H and Spurr C L. Hexamethonium in the chronic treatment of hypertension—Its effects on renal hemodynamics and on the excretion of water and electrolytes. J Clin Invest 32 1133 1953

123 Dustan H P Tarazi R C and Bravo E L. Physiological characteristics of hypertension Am J Med. 52 610 19 2

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REFERENCES

79 Becker Christensen F Burg H O and Ditzel J Treatment of severe hypertension with Catapres (St 155) Acta Med Scand **190** 21 1971

80 Putzeys M R and Hoobler W W Comparison of clonidine and methyldopa on blood pressure and side effects in hypertensive patients Am Heart J **83** 4[illegible] 1972

81 Mroczek W J Leibel B A and Finnerty F A Comparison of clonidine and methyldopa in hypertensive patients receiving a diuretic Am J Cardiol **29** 712 1972

82 Hunyor S N Hansson L Harrison, T S a Hoobler S W Effects of clonidine withdra Possible mechanisms and suggestions for mana Br Med J **2** 209 1973

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84 Ablad B A study of the mechanism of the he namic effects of hydralazine in man Acta Pharm Toxicol **20** (Suppl 1) 1 53 1963

85 Koch Weser J Vasodilator drugs in the treatm hypertension Arch Intern Med **133** 1017 19 4

86 Perry H M Jr Tan M Carmody S and Sak A Relationship of acetyl transferase activ antinuclear antibodies and toxic symptoms in hyp tensive patients treated with hydralazine J Lab C Med **76** 114 1970

87 Zacest R Gilmore E and Koch Weser J Treatm of essential hypertension with combined vasodila and beta adrenergic blockade N Engl J M **286** 617 1972

88 Chidsey C A Gottlieb T B Plus R G O J C and Weil J V The use of vasodilator and be adrenergic blockade in hypertension *in* Hyperten mechanisms and management edited by G O K E Kim and J H Moyer New York 1973 Grune Stratton Inc pp 357 367

89 Chidsey C A and Gottlieb T B The pharmacol basis of antihypertensive therapy The role of vaso lator drugs Progr Cardiovasc Dis **17** 99 19 4

90 Gottlieb T B Katz F H and Chidsey C A Combined therapy with vasodilator drugs and be adrenergic blockade in hypertension—A compar study of minoxidil and hydralazine Circulation **45** 1972

91 Pettinger W A and Mitchell H C Minoxidil alternative to nephrectomy in refractory hypert N Engl J Med **167** 171 1973

92 Hammer J Ulrych M and Freis E D Hemod namic and therapeutic effects of guancydine in hyp tension Clin Pharmacol Ther **12** 78 19

93 Gupta N and Goldberg L I Guancydine a vasodilator Comparison with hydralazine in a re including propranolol and quinethazone *in* Hyperten sion Mechanism and management edited by G Ons K Kim and J Moyer New York 1973 Grune Stratton Inc pp 301 306

94 Johnson B F Diazoxide and renal function in ma Clin Pharmacol Ther **12** 815 1971

95 Beamer V L and McDonald R H Failure of repeated diazoxide injections to modify the course of severe hypertension Am Heart J **79** 47 19 0

96 Landesman R Coutinho E M Wilson K H Lopez A C V The relaxant effect of diazoxide o nongravid human myometrium in vivo Am J Obst Gynecol **102** 1080 1968

97 Fajans S S Floyd J C Jr Thiffault C A R F Harrison T S and Conn J W Further studie on diazoxide suppression of insulin release fro abnormal and normal islet tissue in man Ann N Acad Sci **150** 261 1968

98 Sellers E M and Koch Weser J Protein binding a vascular activity of diazoxide N Engl J Med **281** 1141 1969

99 Miller W E Gifford R W Humphrey D C Vidt D G Management of severe hypertension wit intravenous injections of diazoxide Am J Cardiol **24** 870 1969

100 Finnerty F A Jr Kakaviatos N and Davidov M

The long term effe t of repeated acute reductions of arterial pressure with diazoxide in patients with severe hyperten ion Ann N Y Acad Sci **150** 461 1968

Sellers, E M and Koch Weser J Di placement of warfarin from human albumin by diazoxide and etha crynic mefanamic and nalidixic acids Clin Pharmacol Ther **11** 5 4 19 0

Thurston H and Pohl J E F Development of extrapyramidal symptoms in hyperten ive patients treated with dia oxide Br Med J **3** 4/4 19 3

Palmer F R ard Lassiter K C Drug therapy Sodium nitroprus ide N Engl J Med **292** 94 19 5

Franciosa J A Giulha N H and Limas C J Improved left ventricular function during nitroprusside infu ion in acute myocardial infarction Lancet **1** 650 19

Tuzel I Limjuice I and Kahn D Sodium nitroprussi le in hyperten ive emergencies Curr Ther Res. **17** 55 19 5

Barker M H The blood cyanates in the treatment of hyperten ion J A M A **106** 6? 1936

Frohlich E D Tarazi R C Dustan H P and Page I H The paradox of beta adrenergic blockade in hyperten ion Circulation **37** 417 1968

Wilson D F Watson [illegible] F Piel J S Langley R B and Turner A S Some hemodynamic effects of tra icor (Ciba 9083/Ba) N Zealand J M **68** 145 1968

Winer N Chok hi D S Yoon M S and Freedman A D Adrenergic receptor mediation of renin secretion J Clin Endocrinol Metab **29** 1168 1969

Michelakis A M and McAllister R G The effect of chronic adrenergic receptor blockade on plasma renin activity in man J Clin Endocrinol Metab **34** 386 19

Tarazi R C Long term hemodynamic effects of beta adrenergic blockade in hyperten ion *in* Hypertension Mechanism and management edited by G Onesti, K Kim and J Moyer New York 19 3 Grune & Stratton Inc p 34

112 Stern S Hoffman M and Braun K Cardiovascular responses to carotid and vertebral artery infusions of propranolol Cardiovasc Res. **5** 425 19 1

113 Frohlich E D Dustan H P and Page I H Hyperdynamic beta adrenergic circulatory state Arch Intern Med **117** 614 1966

114 Gorlin R The hyperkinetic heart syndrome J A M A **182** 823 1962

115 Frohlich E D The use of beta adrenergic blockade in hypertension *in* Hypertension Mechanisms and management edited by G Onesti K Kim and J Moyer New York 1973 Grune & Stratton Inc pp 335 336

116 Prichard B N C Propranolol as an antihypertensive agent, AM HEART J **79** 128 19 0

117 Prichard B N C and Gillam P M S Propranolol in hyperten ion Am J Cardiol. **18** 387 1966

118 Waal H J Hypotensive action of propranolol Clin Pharmacol Ther **7** 588 1966

119 Humphreys, G S and Delvin D G Ineffectiveness of propranolol in hypertensive Jamaicans Br Med J **2** 601 1968

120 Wilson A G Brooke O G Lloyd H J and Robinson B F Mechanism of action of β adrenergic receptor blocking agents in angina pectoris Comparison of action of propranolol with dexpropranolol and practolol Br Med J **4** 399 1969

121 Volle R L and Koelle G B Ganglionic stimulating and blocking agents, *in* The pharmacological basis of therapeutics fourth edition edited by L S Goodman and A Gilman New York 19 0 Macmillan Publishing Company Inc pp 585-600

122 Ford R V Moyer J H and Spurr C L Hexame thonium in the chronic treatment of hypertension—Its effects on renal hemodynamics and on the excretion of water and electrolytes, J Clin Invest **32** 1133 19 3

123 Dustan H P Tarazi, R C and Bravo E L Physiological characteristics of hypertension Am J Med **52** 610 1972

on II

Annotations

Malfunction of viscosity-receptors (viscoreceptors) as the cause of hypertension

Blood viscosity remains steady over the short or long period of time in healthy men In effect there are hardly any viscosity differences between young and old healthy men[1] The menstrual cycle is responsible for cyclic viscosity variations in females but blood viscosity becomes steady after menopause or when the female is on the contraceptive pill[2]

The steady level of blood viscosity could be explained as a result of automatic controls exerted by kidney spleen and lungs *via* pH adjustments proteins and hemoglobin production control of CO_2 or O_2 partial pressures However evidence appears which brings some doubt whether the metabolic control and perhaps baroreceptor s control are solely responsible for control of blood viscosity

This becomes evident when one considers that hematocrit is reduced considerably in sickle cell anemia cancer hypothyroid states etc The whole blood viscosity usually remains nearly normal even when plasma viscosity increases (as in macroglobulinemia or myeloma) or when the internal viscosity of the red cell increases Indeed a decrease of hematocrit at increased rigidity of the red cells or at increased plasma viscosity can be regarded as an evidence for the presence of blood viscosity regulation through viscosity receptor or receptors

In order for such a blood viscosity receptor to function it must be able to measure two values the viscosity of whole blood and the internal viscosity (and deformability) of the red cell Let s call the receptor responsible for the first function a viscoreceptor alpha and the receptor responsible for the second function a "viscoreceptor beta Viscoreceptor beta when detecting an increased rigidity of the red cells should influence the setting of the control loop directed by the viscoreceptor alpha that is it should induce viscoreceptor alpha to reduce normal level of blood viscosity and hematocrit

The need for the two receptors becomes obvious if one realizes that the whole blood viscosity is of primary importance in large vessels while the internal viscosity of the blood cells (or a ratio of the internal viscosity of the cell to the viscosity of plasma) is of primary importance in the microcirculation (Fig 1)

In most diseases studied such as sickle cell anemia (in which internal viscosity of the red cell increases greatly), in macroglobulinemia (in which plasma viscosity greatly increases) or in malignant melanoma (in which we see a small increase in plasma viscosity and a small increase in the rigidity of cells) the whole blood viscosity is roughly within the usual limits or even below the normal limits.[3]

An example of the viscoreceptor alpha malfunction could be polycythemia when the whole blood viscosity increases.

A result of malfunction of the viscoreceptor beta could be hypertension In this case the viscoreceptor beta does not carry out an adjustment (decrease of hematocrit) needed to compensate for increased rigidity of the red cells

The microcirculatory system appears to be able to compensate for increased rigidity (increased internal viscosity) of the red cells as long as the number of red cells is reduced however the accommodation to higher rigidity cells has a certain limit (this limit depending also on the elasticity of capillary or arteriolal walls) and it breaks down when the number of cells is too high The inversion phenomenon (in which resistance to flow increases rapidly at a certain critical capillary radius depending on the rigidity of blood cells) acts as an amplification system for increase of the resistance to flow[3]

All these considerations might become clearer when Figs 2 and 3 are consulted These contain means and standard deviations of blood viscosity plasma viscosity and rigidity of red cells (as expressed by the term Tk) for the following disorders diabetes myocardial infarction melanoma leukem

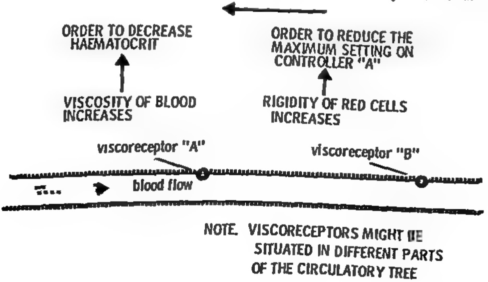

Fig 1 A schema of action of blood viscosity receptors alpha (*A*) and beta (*B*)

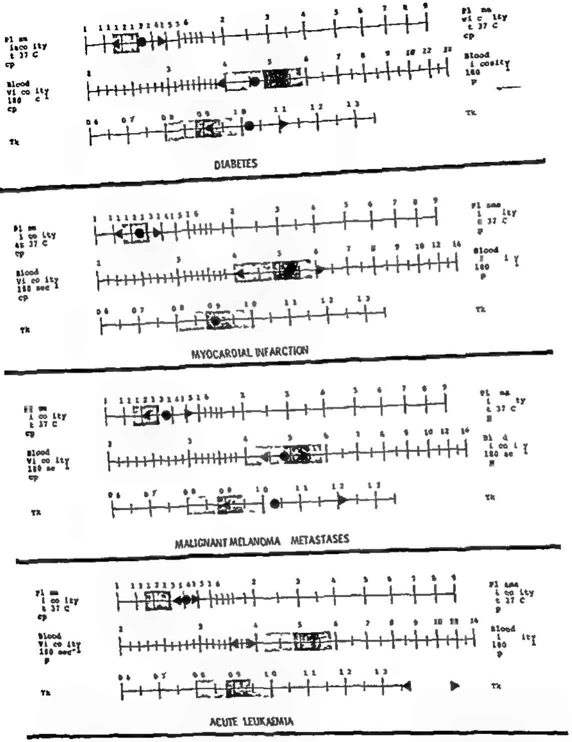

Fig 2 Blood viscosity (at high shear rate) plasma viscosity and rigidity (Tk) of red cells in series of patients with diabetes (n = 30) myocardial infarction (n = 30) melanoma (n = 50) and acute leukemia (n = 3) Dots and arrows indicate means and a range of one standard deviation The shaded area corresponds to normal values when two shaded areas superimpose, the left hand area illustrates means plus/minus one standard deviation for athletes (n = 1[illegible]) and the right hand area shows the same values for healthy normal men (n = 125) Term "Tk" is a coefficient of rigidity of red cells in the blood viscosity *equation* *Note that* increased rigidity of red cells is compensated by *decreased* viscosity of the whole blood mainly due to decreased hematocrit

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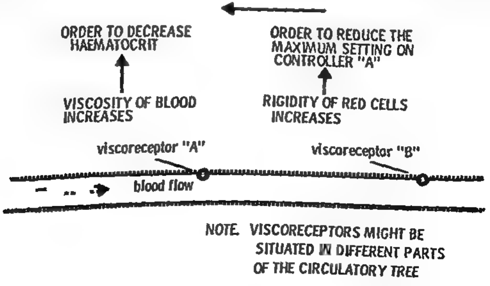

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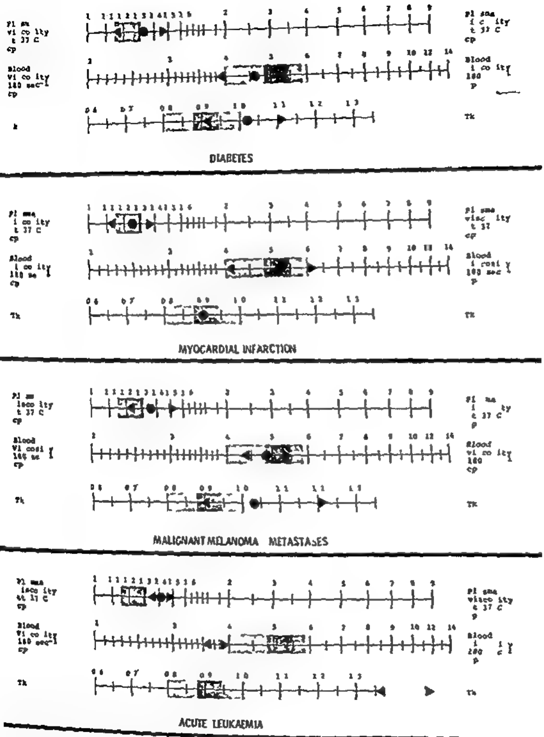

Fig 2 Blood viscosity *(at high shear rate)* plasma viscosity and rigidity (Tk) of red cells in series of patients with diabetes (n = 30) myocardial infarction (n = 30) melanoma (n = 30) and acute leukemia (n = 3) Dots and arrows indicate means and a range of one standard deviation The shaded area corresponds to normal values when two shaded areas superimpose the left hand area illustrates means plus/minus one standard deviation for athletes (n = 1) and the right hand area shows the same values for healthy normal men (n = 125) Term "Tk" is a coefficient of rigidity of red cells in the blood viscosity equation Note that increased rigidity of red cells is compensated by *decreased* viscosity of the whole blood mainly due to decreased hematocrit

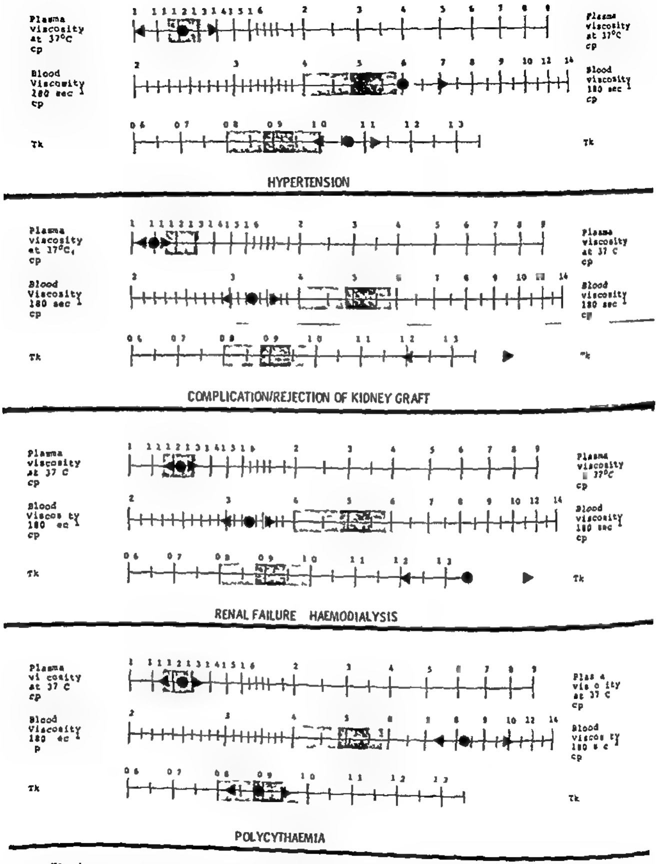

Fig 3 *Blood viscosity (at high shear rate) plasma viscosity and rigidity (Tk) of red cells in series of patients with hypertension* (n = 30) *kidney transplantation and renal failure* (n = 32) *and polycythemia* (n = 12) Note that increased rigidity of red cells in hypertension is not compensated by decreased viscosity of whole blood such compensation is clearly shown in the renal series (although it does not have to be a complete or satisfactory compen… other type of viscosity abnormality is shown by polycythemia in which both the plasma viscosi… of red cells appear to be within normal limits

ypertension renal failure and kidney transplantation and cythemia In all cases when an elevation of the internal osity (rigidity) of the red cell is observed a compensation hieved by a decrease in the viscosity of the whole blood one exception that of hypertension

It is suggested that an associated cause of hypertension (or haps one of the types of hypertension) is the presence of viscosity (low deformability) blood cells notwithstanding the fact that the viscosity of whole blood might be slightly elevated or be staying even without normal its. It would be a compensatory function of baroreceptors allow an increase of blood pressure in order to push a large nber of these cells through the microcirculation

The question will then be asked what is the action of antihypertensive drugs? These drugs showed in a most cessful manner that blood pressure can be reduced and a ient can expect a nearly normal life pan

My answer is that unbeknownst to drug makers or drug rs, the antihypertensive drugs do reduce the internal cosity of the blood cells Their action on the baroreceptors ght or might not really exist

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REFERENCES

1. Dintenfass, L Julian D G and Miller G Viscosity of blood in normal subjects and in patients suffering from coronary occlusion and arterial thrombosis AM HEART J 71 587 1966
2. Dintenfass, L Blood microrheology viscosity factors in blood flow ischaemia and thrombosis London 1971 Butterworth & Co Ltd
3. Dintenfass, L and Read J Pathogenesis of heart failure in acute-on-chronic respiratory failure Lancet 1 570 1968
4. Dintenfass L Blood rheology in pathogenesis of the coronary heart disease AM HEART J 77 139 1969
5. Dintenfass L Internal viscosity of the red cell and a blood viscosity equation Nature (Lond) 219 956 1968
6. Dintenfass, L The internal viscosity of the red cell and the structure of the red cell membrane Considerations of the liquid crystalline structure of the red cell interior and membrane from rheological data Molecular Crystals—Liquid Crystals 8 101 1969
7. Dintenfass, L Internal viscosity of the red cell problems associated with definition of plasma viscosity and effective volume of red cells in the blood viscosity equation Biorheology 12 253 1975

Transient right bundle branch block with Swan Ganz catheterization

Bedside right heart catheterization with flow-directed balloon tipped catheters (Swan Ganz catheterization) is not wholly free of complications. Recent reports have emphasized distal migration of the catheter with pulmonary arterial damage or infarction However rhythm disorders are reported to be less frequent when catheters are flow directed an important facet of their utility in acute myocardial infarction Presumably the catheter tip is protected from irritating the right ventricular endocardium by the inflated balloon To our knowledge conduction defects have not been among the rhythm disturbances reported with this procedure.

We have recently observed the occurrence of right bundle branch block (RBBB) in three patients during blind passage of a balloon inflated catheter through the right ventricle (Table I) During the period of observation 4 blind catheterizations were performed with balloon tipped catheters Thirty-eight were via an antecubital vein for hemodynamic monitoring mostly in acute myocardial infarction and nine were via a femoral vein for temporary pacemaker insertion RBBB was seen only with the antecubital approach to the pulmonary artery or wedge positions The duration of block ranged from 3 to 36 hours In each instance block was unassociated with other conduction defects or change in cycle length Only two of the patients had anteroseptal myocardial infarctions The conduction defect disappeared in all three while the catheter remained positioned in the pulmonary artery Adequate pressure monitoring was achieved throughout and there was no radiologic evidence of distal migration of the catheter or pulmonary infarction

Transient RBBB is a well recognized complication of right heart catheterization The purpose of this communication is

Table I RBBB with Swan Ganz catheterization

No	Age	Sex	Diagnosis	Duration (hr)	Other sequelae
1	49	F	Acute anteroseptal infarction	3	None
2	56	M	Acute pericarditis	5	None
3	50	M	Acute anteroseptal infarction	36	None

to emphasize that the use of an inflated balloon tipped catheter for blind passage through the right ventricle might not prevent this complication The catheter tip may not be the cause of mechanical damage to the right bundle branch Trauma to the bundle might result as well from a rigid catheter loop fixed both at the site of venous introduction and at the site of pulmonary arterial occlusion

The occurrence of RBBB with Swan Ganz catheterization should not be considered evidence for pulmonary thrombosis caused by distal migration of the catheter In our patients the transient RBBB was of no clinical significance However the danger of induction of RBBB must be considered in the bedside catheterization of patients with pre existing left bundle branch block or with acute anteroseptal myocardial infarction

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REFERENCES

1 Foote G A Schabel S I and Hodges M Pul... complications of the flow directed balloon tipped ca... ter N Engl J Med 290 9?7 1974
2 Golden M S, Pinder T Jr Anderson W T a... Cheitlin M D Fatal pulmonary hemorrhage comp... ting use of a flow-directed balloon tipped cath... a patient receiving anticoagulant therapy Am J Car... 32 865 1973
3 Swan H J C and Ganz W The use of balloon tip... flow directed catheters in monitoring patients with a... myocardial infarction *in* Corday E and Swan H J ... editors Myocardial Infarction Baltimore 19... Williams & Wilkins Company
4 Swan H J C Ganz W Forrester J Marcus ... Diamond G and Chonette D Catheterization of ... heart in man with use of a flow-directed balloon ... catheter N Engl J Med 283 447 1970
5 Voukydis P C and Cohen S I Catheter ... arrhythmias AM HEART J 88 588 1974
6 Meister S G Banka V S and Helfant R H Tra... femoral pacing with balloon tipped catheters, J A M A 225 712 1973
7 Mendel D A practice of cardiac catheterization Oxford 1975 Blackwell Scientific Publications

Of the heart-to-chest ratio

It has been the practice over many years for radiologists and cardiologists to determine cardiac enlargement from the ratio of the maximal transverse diameter of the heart to the maximal transverse internal diameter of the chest obtained from the teleoroentgenogram When this ratio exceeds 50 per cent (actually 57 per cent) the heart is considered to be large Yet adequate consideration is not always given to patients whose chest size shrinks with age The senile chest is associated with shrinkage and change in shape with age For example Fig 1 shows the teleoroentgenogram of the chest of a 78 year old lady Is her heart really enlarged producing an abnormally great ratio of heart to chest diameter or is this ratio abnormal because the chest has shrunk in size and changed shape with age without enlargement of the heart or have both changes occurred to some extent? The heart shadow appears to be normal in size for the lady of 5 ft 4 in in height weighing 132 pounds Should the heart be expected to shrink with age and if so at what rate and degree? After all the heart exercises all the time so that its muscle mass is used constantly The heart muscle is not at disuse If there is no atrophy of disuse there may be atrophy of less use Finally can the heart normally enlarge a little and the chest cage shrink some with age? If so what are the standards? With degeneration of some myocytes with age there may be

Fig 1 Teleoroentgenogram of a 78 year old female patient apparently showing an abnormally great ratio of heart to chest diameter (see text)

k hypertrophy of the remaining myocytes which must rm the necessary cardiac work

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REFERENCE

1 Burch, G E Interesting aspects of geriatric cardiology Am Heart J 89 99 1975

ecialization—Another tiger by the tail

at is a cardiologist? The definition was formerly straight ward and simple A cardiologist was a physician with cial knowledge of the heart and its diseases (from the Greek dia for heart + logia the study of) Within this medical cialty however a rapid expansion of knowledge together h an increasing fragmentation of interests have occurred r the last 20 years Present day technology permits one to ve into and probe all orifices internal organs secretions, l cells of the body with a vast array of equipment further petuating this cycle of increasing sub pecialization Start with a cardiologist generalist Fig 1 might be considered representing how this area of medicine has become further ctionated into subspecialties and subinterests

This progressive involvement with more complex but rrower areas of interest creates a greater dependence upon propriately trained physicians, skilled technical assistants, creasingly sophisticated equipment and suitable and lequate patient referral In so doing it gives rise to numerous estions and problems, such as (1) Where is the support articularly financial) to come from both for equipment and rsonnel? (2) Is the trained technical assistance available?) What size community can support which procedures? How is this to be decided? (4) What determines the volume of patients that is desirable so that proficiency in any particular area can be acquired and maintained? How is the quality of performance to be monitored? (5) If available resources are limited, how are they to be distributed? Is this to be by chance dependent only upon the interest or financial capability of a hospital or community? Or are there other ways of deter mining this?

In an effort to apply knowledge and technology to beneficial use in a rational realistic advantageous and nonwasteful fashion it is hoped that the medical academic and govern mental worlds can combine their wisdom and experience to arrive at workable solutions to these and like questions. It is also to be hoped that this increasing subspecialization and its attendant desirable features will not be at the expense of direct and personal communication between physician and patient especially in the area of heart disease where this relationship is so vital and important in management and therapy

pported in part by a grant from the G trud H [illegible] gers F nd.

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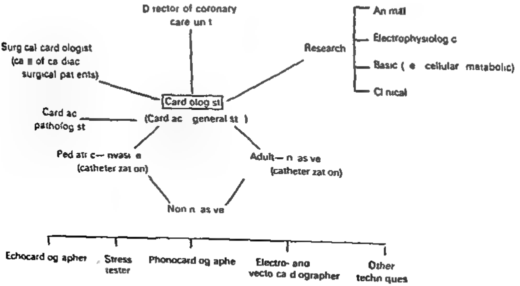

Fig 1 Fractionation of cardiology

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1 Foote G A Schabel S I and Hodges, M Pu... complications of the flow directed balloon tipped c... ter N Engl J Med 290 927 1974
2 Golden M S., Pinder T., Jr Anderson, W T ... Cheitlin M D Fatal pulmonary hemorrhage comp... ting use of a flow directed balloon tipped catheter i... patient receiving anticoagulant therapy Am J C... 32 865 1973
3 Swan H J C and Ganz W The use of balloon-tip... flow-directed catheters in monitoring patien... w... myocardial infarction in Corday E and Swan H J C editors Myocardial Infarction Baltimore, 1973 Williams & Wilkins Company
4 Swan H J C Ganz, W Forrester J Marcus ... Diamond G and Chonette D Catheterization of heart in man with use of a flow-directed balloon-tip catheter N Engl J Med 283 447 1970
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upported in part by a gra t from the Gertru l H Rogers F d.

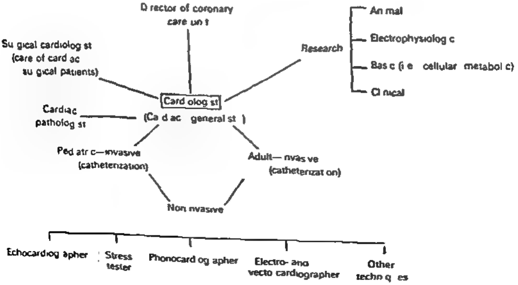

Fig 1 Fractionation of cardiology

Letters to the Editor

Soup? It may be hazardous to your health!

To the Editor

Dr George E Burch (AM HEART J 91 267 1976) very aptly describes soup as containing everything one finds in plant and animal tissues and as being the ideal replacement fluid true—if it is home made that is Industrially prepared soups contain all those ingredients and then some Rarely is soup nowadays truly home made Whether served in restaurants homes or hospitals it s mostly prefabricated and 20 000 tons of Monosodium Glutamate are dumped into such soups annually in the U S Very few commercially prepared soups are without it because of its effect on the taste and quantitatively it is the most widely used food additive The harmfulness of MSG to children is acknowledged and it has been barred from baby foods Its effects on adults are accepted as a curious nuisance which susceptibles may avoid by keeping a respectful distance from Wonton soup Experiments have pinpointed the symptoms susceptibles develop such as burning sensations and substernal pain However these experiments were done on healthy adults and not on people with cardiovascular disorders

I have seen reactions involving frequent ventricular premature beats and considerable discomfort beginning shortly after eating in a Chinese restaurant None of the other common sensations were present but the arrythmia continued for hours and triggered a lengthy period of reduced functional capacity of the heart

Sometimes there is an easy clue which may draw attention to the link such as the preceding consumption of Chinese food while other such incidents with similar unpleasant responses can be traced to MSG if histories include such questions

In patients with a tendency to episodic arrhythmias it is worthwhile to explore whether before such an attack they had consumed food items possibly containing Monosodium Glutamate Commercially prepared soups are suspect not just Chinese dishes and while most brands of soups contain substantial amounts of MSG little of it (a gram) can be enough to produce reactions in susceptibles

Because sensitivity to MSG is not rare and because of the unpredictable consequences given a damaged vulnerable or irritable myocardium patients with a tendency to rhythm disturbances should be made wary of prefabricated soups and meat tenderizers in addition to the fare of Chinese restaurants

Incidentally the term Chinese restaurant syndrome while picturesque is too narrow considering the tons of MSG used in less exotic foods The syndrome should really be termed what it is an MSG atopy And the cardiovascular system is its chief target

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1 Schaumburg H H Byck R Gerstl R et al Monosodium L glutamate Its pharmacology and role in Chinese Restaurant Syndrome Science 163 826 1969

Risk factors and coronary heart disease

To the Editor

Werko s review (AM HEART J 91 87 1976) omits the factor we have found most useful in the rehabilitation patients with coronary heart disease That risk factor is sedentary living A significant degree of risk reduction is associated with the vigorous life style "Mileage covered on foot" is one index of this vigor Populations which cover twenty kilometers a day on foot burn approximately 1 kcals and have very little atherosclerosis This is noted in the Masai warriors who herd cattle on foot and the Tarahumara Indians who take part in ceremonial runs Longevity is associated with mileage Extreme examples of longevity have been reported among the Hunza and other remote mountain villagers who must walk a great deal[3] Longshoremen who burned 1 800 kcal per day show reduced heart disease This is the caloric equivalent of 30 Kms We have been unable to substantiate a single atherosclerotic death among marathon runners The marathon run is 42 Kms in length and suitable activity for rehabilitated heart patients.

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REFERENCES

1 Ho K J Biss K Mikkelson B et al The Masai East Africa Some unique biological characteristics Arch Pathol 91 387 1971
2 Groom D Cardiovascular observations on Tarahumara Indian runners—the modern Spartans Am Heart J 81 304 1971
3 Leaf A Unusual longevity The common denominator National Geographic 143 93 1973 (January)
4 Paffenbarger R S and Hale W E Work activity and coronary heart mortality N Engl J Med 292 1975
5 Bassler T J Steiner R and Cardello F Marathon distance running N Engl J Med 294 114 1976.

Reply

To the Editor

It is obvious that Dr Bassler has not understood the purpose of my review—to point out difficulties and flaws in well known extensively published studies I am however grateful to him for his remarks as this gives me opportunity to point out that there are no controlled studies that support the statement in the letter On the contrary it is quite clear that athletes and especially marathon runners and cross-country skiers are a self selected group with quite different physical and mental make up compared to the general population. It is thus impossible to draw any conclusions from such anecdotal evidence that Dr Bassler cites It is furthermore not at all clear that athletes have a better cardiovascular health than other groups Studies in Finland and Sweden have been rather disappointing in this respect

A controlled study of the effect of standardized physical training after myocardial infarction that was done in Goteborg also demonstrated the slight gain in comparison to for example stopping smoking cigarettes The marathon

ers club ought to try to study the problem in a scientific and not act only on belief

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Sanne H Exercise tolerance and physical training of non selected patients after myocardial infarction Acta Med. Scand Suppl 551 1973

ncerning the etiology of atherosclerotic art disease

the Editor

The AMERICAN HEART JOURNAL has always been one of the rnals I look forward with pleasure to receiving each month in the distant recesses of the United States, the Sandwich ands. I particularly appreciated Dr Wheatley s editorial in June issue and was somewhat amused at the response of Eskwith in the JOURNAL (AM HEART JOURNAL 90 809 5)

It seems that with each passing year and the further cumulation of information medicine (or more particularly ysicians) become more and more hysterical as they vainly y to preserve totems that they fervently believe in i e the k taking life style For indeed, failure to do otherwise ould necessitate a change both in their personal and profesonal lives rather than to admit that they are living a life of lf indulgence with the attendant morbidity and mortality ccompanying such an absurd pattern of behavior Dr skwith neatly sidesteps the overwhelming amount of statistical data associated with the detriment of cigarette smoking pace does not permit (especially since most of it has already een published in your own Journal) the innumerable effects of nicotine on the entire cardiovascular system Dr Eskwith lso lumps all athletes into one category which is as simplistic s saying that Negroes Orientals, and Caucasians all being humans have exactly the same spectrum and percentages of ach given disease Athletes engaging in isometrics have a life expectancy shorter than the standard whereas long distance runners have a definitely decreased incidence of coronary mortality You are well aware I am sure that *The New England Journal of Medicine* October 30 19 5 reported several cases of fatal myocardial infarction occurring in long distance runners confirmed by autopsy I think it interesting that in personal correspondence with physicians reporting these cases, initial replies were that a myocardial infarction had not been confirmed and finally they admitted that in each of the cases that they had reported a postmortem had not been done Yet it seems that we are all so eager to rush into print (and the journals are so willing to publish this data) that rumors are being published as documented fact rather than being further investigated Dr Jeremy Morris at a recent international symposium on cardiovascular disease in Toronto stated that because of all of the variables involved the appropriate study confirming or denying whether exercise had a protective benefit could no longer be done The size of the population, the variables that would require control, and the expense preclude this absolute insight so necessary to Dr Eskwith's dialogue. At the same time Dr Morris stated that he felt that the body of evidence albeit circumstantial, was so overwhelming that abstinence from tobacco and appropriate exercise were a necessary part of every physician s therapeutic armamentarium

In our own experience over the past six years in Honolulu (approximately 17 000 maximum treadmill stress tests and one of the largest Cardiac Rehabilitation Programs in the United States) we have seen several people die of myocardial infarction Interestingly enough all were smoking up to the time of the infarction and those in Cardiac Rehabilitation Program who had discontinued smoking, irrespective of the severity of the disease all are alive and well today

Rather than the regimens of deprivation of food abstinence from tobacco and forced exercise fading into oblivion it more likely will be physicians such as Dr Eskwith Although I laud his ambition to make everyone rich, we have found our own appointment books progressively becoming busier and busier with patients who are sick and tired of being told to take it easy and that cardiovascular disease at an early age is inevitable We laud Dr Eskwith and his colleagues as being beneficial to our own form of practice

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Reply

To the Editor

Thank you for permitting me to reply to the above letter Dr Scaff's idea that one type of exercise is beneficial and another harmful is too mystical a concept for me to accept Circumstantial evidence no matter how strong has no place in scientific discipline and cannot be substituted for proof neither can anecdotal reports. Dr Scaff s letter however does illustrate the intense amounts of emotion which go into some cardiologists feelings concerning the etiology of heart disease

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A V conduction in children

To the Editor

The article entitled Patterns of atrioventricular conduction in children (AM HEART J 90 165 August 1975) is of great interest to those of us performing intracardiac electrocardiography in children We feel however that the values obtained in this study are inaccurate because of the sedation used on their patients.

It is of note that most adult centers perform His bundle electrograms on patients in the postabsorptive *non sedated state* or with barbiturate sedation This caused some concern on our part as it is difficult to perform cardiac catheterizations on most children without adequate sedation We have noted

Table I Effects of sedation on cardiac performance

	AH interval (msec)	Induced Wenckebach block (intervals in msec)
Resting	150	690
Isuprel (mgm /min)	70	465
CM3	90	295

that the sedative mixture we use (Demerol Phenergan and Thorazine) regularly produces a mild tachycardia in all patients undergoing catheterization Our awareness of the cardioaccelerating properties of this sedation was dramatically increased when a patient with a non paroxysmal junctional tachycardia arising in the right bundle developed a sinus tachycardia completely obscuring the dysrhythmia after receiving sedation prior to His bundle studies

Subsequent to this all patients for His bundle studies have been sedated with Nembutal The effect of the Nembutal lasts for 1½ to 2 hours In one patient normal sedation was given after being studied for prolonged A V conduction the results described in Table I amply illustrate our point

It is obvious that A V conduction times decreased and atrioventricular conduction of rapid stimulation was markedly enhanced by the administration of a mixture of Demerol Phenergan and Thorazine

It is our opinion that cardiac refractory periods in children obtained while under sedation with Demerol Phenergan and a chlorpromazine like substance are not accurate

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Reply

To the Editor

We appreciate Dr Sapire's concern that the electrograms which we reported may not have been obtained under basal conditions but were influenced by premedication The information on Dr Sapire's patient is interesting but in well over 3 000 cardiac catheterizations we have not observed significant sinus tachycardia following Demerol Phenergan and Sparine sedation You will note that in our study the heart rate of 20 cases was within the normal range for age and in two cases only (cases 3 and 4) it was above the 95th percentile Although chlorpromazine and promethazine can produce a mild tachycardia due to their slight atropine-like effect, the changes are minimal compared to the fact that basic electrophysiologic intervals and refractory periods lengthen with increasing age Human refractory periods are directly related to cycle length except for A V nodal effective refractory period which is inversely related The relationship between change in atrial functional refractory period and A V nodal effective refractory period in response to variation in cycle length is such that the atrium may limit the determination of A V nodal effective refractory period at long cycle lengths, but this is less likely at short cycle lengths. In our study the atrium was the limiting structure in 11 of the 20 cases. Other authors have confirmed this finding[3,4] that these responses appear to be age related and that heart rate seems to be a much less important factor We believe that our own data and the widely reported data of others amply confirm the validity of electrophysiologic measurements obtained using chlorpromazine promethazine and meperidine types of premedication Although the first two may occasionally produce tachycardia (meperidine does not change the heart rate), and although Nembutal may very occasionally produce sinus tachycardia monitoring of the pulse rates of these children before and during the procedure and comparing them with the normals for their age should alleviate these concerns

In conclusion we believe that even though there may be some limitations to electrophysiological studies in children related to apprehension and mild sedation we stand by the accuracy of our measurements (the variability was within ± 2 5 msec) and their clinical value in the diagnosis and treatment of children with rhythm disturbances

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REFERENCES

1 Goodman L S and Gilman A The pharmacological basis of therapeutics Fifth Edition New York, 19[illegible] McMillan Publishing Company Inc
2 Moss A and Adams F H Heart disease in infants children and adolescents Baltimore 1968 The Williams & Wilkins Company
3 Abella J B Teixeira O H P Misra K P and Hastreiter A R Changes of atrioventricular conduction with age in infants and children *Am J Cardiol* 30 [illegible] 1976
4 DuBrow I W Fisher E A Denes P and Hastreiter A R The influence of age on cardiac refractory periods in man Pediatr Res 10 135 1976
5 Denes P Wu D Dhingra R Pietras R J and Rosen K M The effects of cycle length on cardiac refractory periods in man Circulation 49 32 1974
6 DuBrow I W Fisher E A Amat Y Leon F Denes P Wu D Rosen K M and Hastreiter A R Comparison of cardiac refractory periods in children and adults Circulation 51 485 1975

Current Status of Cardiac Surgery Edited by D B ngmore Baltimore 1975 *University Park Press*, 507 pages, ce $39.50

This book should interest cardiologists as well as surgeons. e former use surgery as a therapeutic procedure in their tients and should be informed at all times of the indications d role of surgery in cardiac therapy Longmore however tes in his support of surgery What is perhaps worse in this failure to apply heart transplantation has been its favorable reception. It is a reasonable and satisfactory ocedure with good results for this early stage in its develop nt, despite the horrendous mortality rate This inter ting point of view was compared by Longmore with early periences with valve surgery and other types of cardiac rgery Nevertheless, this provocative statement established e stage for the Fifth Cardiac Surgical Course held in ondon. The program was a teaching course rather than a mposium Many outstanding surgeons discussed cardiac *ansplantation, tetralogy of Fallot prosthetic valves cardiac* urgery in infants, surgery for ischemic heart disease and for re forms of congenital heart disease Cardiologists and rdiac surgeons in training should find this book an inter sting one and even worth owning, in spite of the fact that *ardiac surgery is changing rapidly*

ulmonary Emboli Edited by Arthur A Sasahara Edmund Sonnenblick, and Michael Lesch, New York, 1975 Grune & tratton Inc., 175 pages. Price $16 50

This is a bound publication of several issues on the subject n the journal, *Progress in Cardiovascular Diseases* Those who already receive the journal will also find this to be a convenient volume to own anyway Pulmonary embolism is in important and common problem in medicine The discussions are primarily from the practical clinical points of view The many contributors review the subject from aspects of etiology pathophysiology diagnosis and treatment This is a good and useful publication

Adult Fitness and Cardiac Rehabilitation Edited by Philip K Wilson EdD Baltimore 1975 University Park Press, 408 pages. Price $19.50

This book represents the papers presented on cardiac rehabilitation at a symposium in the spring of 1974 As in all the symposia of present times many papers are presented and discussed by contributors from many areas of the world The subject of physical fitness and cardiac rehabilitation are of great importance in cardiology The discussions vary from discussions of interest to investigators to those that interest physicians in the practice of medicine The use of exercise in testing cardiac function is presented along with underwater weighing to determine physical fitness The book edited by Wilson should interest people in YMCA programs and college and university training programs more than it will physicians and physiologists.

A Commonsense Approach to Coronary Care—A program 2nd ed By Marielle Ortiz Vinsant RN Martha I Spence RN and Dianne Chapell Hagen RN St Louis, 1975 The C V Mosby Company 258 pages. Price $ .5

This paperback book is a self instruction course for nurses who work in coronary care units. Nurses will find this to be a good source of study material The presentations are simple and are designed to quiz the reader as she or he progresses with the study of the book. Certainly the material is oversimplified nevertheless, the simplifications assist the beginner in under standing cardiac function and disease The illustrations, testing scheme, and bibliographies are good *Nurses should* find this to be a useful book and a good source of study

Atrial Fibrillation—Etiology Course and Prognosis A Follow-up Study of 1212 Cases. By John Godtfredsen Copenhagen, 1975 Universitetets Annex auditorium A., 242 pages.

This paperback book of 242 pages is devoted to the study of 1 212 patients with atrial fibrillation As might be expected, this is a rather extensive consideration of a single disturbance in heart beat. Godtfredsen divided the book into seven chapters which are concerned with review of the literature methods and materials, general survey of the patient material, course of atrial fibrillation prognosis, and general concluding remarks. This is a very good single source of material on an important and common disturbance in cardiac rhythm The book is probably the most thorough review and study of atrial fibrillation available.

An Introduction to Pediatric Cardiology By William B Strong, MD Maurice Levy EdD Dorothy Tompkins M.D., and Myron J Adams, MD Springfield Ill, 1975 Charles C Thomas, Publisher

This compendium on pediatric cardiology is presented with simple diagrams and legends to instruct the beginner Concepts in the fetal and post natal circulations are presented by simple illustrations. The congenital defects with the associated disturbances in the cardiac and peripheral circulations are graphically illustrated by means of conventionally accepted diagrams used in discussing congenital heart disease and supported by simple legends. Undergraduate medical students will find this to be a useful source for study even though it is extremely brief The subject is important and should be known to some extent by the family doctor as well as by all general pediatricians

Pulmonary Thromboembolism By Kazi Mobin Uddin MBBS Springfield Ill, 1975 Charles C Thomas, Publisher 393 pages, Price $40 00.

This volume represents proceedings of a symposium on new concepts of pulmonary thromboembolism The contributors are from various medical centers in the U.S.A Although the symposium was supposed to be concerned with new concepts this reviewer was unable to find them unless the definition of new includes developments in the last decade and includes such subjects as the use of drugs to prevent platelet sticking low dose heparin prophylaxis, and use of scanning technics for early diagnosis of deep vein thrombosis. Regardless this book does review in a single source the present-day policies in the diagnosis and treatment of thromboembolic disease states. Pathogenesis, pathophysiology diagnosis, prevention and treatment are thoroughly discussed Medical students house staff and all physicians will find this to be a useful book It provides them with an opportunity not only to learn but to determine whether or not their management of thromboembolism conforms to present-day standards.

Books received

Computer Analysis of the Electrocardiogram By Hubert V Pipberger M D Leiden The Netherlands 1975 Leiden University Press 22 pages

Folia Anatomica Iugoslavica Sixteenth Congress of the Yugoslav Association of Anatomists Sarajevo Yugoslavia 1975 Department of Anatomy Medical Faculty 152 pages

Organ Physiology—Structure and Function of the Cardiovascular System 2nd edition By Robert F Rushmer Philadelphia 1976 W B Saunders Company [illegible]49 pages

Announcements

National Joint Stroke Conference

The Stroke Council of the American Heart Association is sponsoring the second annual National Joint Stroke Conference to be held on February 25 and 26 1977 at the Sheraton 4 Ambassadors Hotel Miami Florida The conference will be held in conjunction with the Cerebrovascular Surgery Section American Association of Neurological Surgeons Canadian Stroke Society Canadian Heart Association and the Society for Vascular Surgery Conference Chairman will be Robert C Siekert M D of the Mayo Clinic

Members of the Stroke Council and others interested in diseases of the cerebral circulation and the physiology and pathological changes in the cerebral circulation are encouraged to submit abstracts to the Program Committee for their consideration Abstracts accepted for presentation will be published in the January 1977 issue of the AHA journal *Stroke* The deadline for receipt of all abstracts is September 1 1976

Guidelines and further information may be obtained from Administrator Postgraduate Courses American Heart Association 7320 Greenville Avenue Dallas Texas 75231

Pan American Congress of Orthopedics and Traumatology

The First Pan American Congress of Orthopedics and Traumatology and the Second International Cinematographic Review of Orthopedics and Traumatology will be held in Acapulco Mexico from October 30 to November [illegible] to promote a scientific and cultural exchange among [illegible] orthopedists and traumatologists The congress is [illegible] by the principal orthopedic associations of the [illegible] Academic activities will include round tables free communications scientific expositions and audio visual sessions with films and slides Educational activities will take place [illegible] during and after the congress course and there will be [illegible] for socio cultural function

We urge all who are interested in attending the congress [illegible] write the congress offices before July 30 1976 Please write [illegible] Pan American Congress of Orthopaedics and Traumatology Paseo de la Reforma No 445 4th floor Mexico 5 DF Telephone 511 64 38 or 511 97 32

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iam J Mroczek M D
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pediatric literature is replete with articles erning the primary prevention of atheroscle s and the identification of ri k factors contrib ig to cardiovascular disease[1,2] However after individual leaves the realm of the pediatri .i usually at puberty there ■ no concerted rt to identify risk factors to stress disease vention or to alter life styles in this popula 1 at risk When the adult cardiologist reflects on our current practices of preventative cardi gy it brings to mind the middle aged male who about to undertake an exercise program of ging or a similar activity Recalling the phasis on primary preventions of the pediatric diologists[3] there appears to be a hiatus in the ucation of the public at a time when life tterns are being established and adult habits being formed At the present time probably e most significant effort being expended upon e health habits of young adults ■ by the lvertising of the tobacco industry[4]

For many years high school health education ograms have been dominated by course work in utrition and infectious diseases This emphasis is nderstandable since these programs were esigned to disseminate information regarding ie leading preventable causes of morbidity and mortality in the 1940 s and 1950 s A review of the health curriculum in the high schools in the metropolitan Washington D C area revealed that approximately only 10 to 15 per cent of the course work was allocated to cardiovascular disease and cancer This is in contrast to the fact that cardiovascular disease stroke and cancer account for 70 per cent of all deaths in the United States Is it not time that health education curricula be re evaluated in light of present health problems? It is common practice that health education in high schools ■ combined with driver s education and physical education and the instructor for many health courses ■ frequently the gym teacher or the football coach Although these individuals may be well qualified in the dissemination of information regarding physical fitness health care education is too important to have it entrusted to a person with no formal medical training The complexities and con troversies of cardiovascular risk factors are not beyond the comprehension of today s high school student however it must be presented to the students by someone who has had formal medical training and can competently answer the ques tions which will invariably be raised Perhaps the title of the course work— Health, is a euphe mistic anachronism of what should be entitled Disease prevention or at least The mainte nance of health and the prevention of disease

In the past year I have addressed numerous high school student bodies regarding the hazards of hypertension and the significance of hyperten sion as a cardiac risk factor I have found the students remarkably receptive to cardiovascular

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pedıatrıc lıterature ıs replete wıth artıcles cernıng the prımary preventıon of atheroscle s and the ıdentıfıcatıon of rısk factors contrıb ıg to cardıovascular dısease . However after ı ındıvıdual leaves the realm of the pedıatrı n, usually at puberty there ıs no concerted ort to ıdentıfy rısk factors to stress dısease ventıon or to alter lıfe styles ın thıs popula n at rısk. When the adult cardıologıst reflects on our current practıces of preventatıve cardı ogy ıt brıngs to mınd the mıddle aged male who about to undertake an exercıse program of ggıng or a sımılar actıvıty Recallıng the nphasıs on prımary preventıons of the pedıatrıc ırdıologısts there appears to be a hıatus ın the lucatıon of the publıc at a tıme when lıfe ıtterns are beıng establıshed and adult habıts re beıng formed At the present tıme probably ıe most sıgnıfıcant effort beıng expended upon ıe health habıts of young adults ıs by the dvertısıng of the tobacco ındustry[1]

For many years hıgh school health educatıon ırograms have been domınated by course work ın ıutrıtıon and ınfectıous dıseases Thıs emphasıs ıs ınderstandable sınce these programs were lesıgned to dıssemınate ınformatıon regardıng he leadıng preventable causes of morbıdıty and mortalıty ın the 1940 s and 1950 s A revıew of the "health currıculum" ın the hıgh schools ın the metropolıtan Washıngton D C area revealed that approxımately only 10 to 15 per cent of the course work was allocated to cardıovascular dısease and cancer Thıs ıs ın contrast to the fact that cardıovascular dısease stroke and cancer account for 70 per cent of all deaths ın the Unıted States. Is ıt not tıme that health educatıon currıcula be re-evaluated ın lıght of present health problems? It ıs common practıce that health educatıon ın hıgh schools ıs combıned wıth drıver s educatıon and physıcal educatıon and the ınstructor for many health courses ıs frequently the gym teacher or the football coach Although these ındıvıduals may be well qualıfıed ın the dıssemınatıon of ınformatıon regardıng physıcal fıtness health care educatıon ıs too ımportant to have ıt entrusted to a person wıth no formal medıcal traınıng The complexıtıes and con troversıes of cardıovascular rısk factors are not beyond the comprehensıon of today s hıgh school student however ıt must be presented to the students by someone who has had formal medıcal traınıng and can competently answer the questıons whıch wıll ınvarıably be raısed Perhaps the tıtle of the course work— Health ıs a euphe mıstıc anachronısm of what should be entıtled Dısease preventıon or at least The maınte nance of health and the preventıon of dısease

In the past year I have addressed numerous hıgh school student bodıes regardıng the hazards of hypertensıon and the sıgnıfıcance of hyperten sıon as a cardıac rısk factor I have found the students remarkably receptıve to cardıovascular

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Recei ed for publıcatıon Oct 1 1975.

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health information and eager to learn It was surprising to me, however, that these students were remarkably deficient in health care information The difference between a "heart attack" and a "stroke" was not clear in the minds of many students It is inconceivable that these students who are capable of taking entrance examinations for college, who are well versed in trigonometry, algebra, geometry and calculus, who know all of the political figures involved in the Watergate scandal, etc, do not have any grasp of such things as cardiac risk factors or elementary concepts of heart attacks, strokes, or cancer Students in high school today are more aware of many aspects of modern society than students in the past generations The political, economic, and sociological aspects of a dictator being overthrown in a far off land could be intelligently discussed with most high school students, however, how many students are aware of the cardiovascular risks of cigarette smoking? Or of the relationship of hypertension to premature death? Or of the association of serum cholesterol levels and coronary artery disease? High school students have the capability of comprehending such medical information, are eager to learn and the high school "health curriculum" is a structural environment where factual medical information could be readily disseminated

In addition to altering habits and influencing life styles of the high school students themselves improved education in disease prevention would have profound ramifications upon the other family members of the students Besides dissemination of information regarding cardiovascular risk factors other useful health care information could readily be included in the health curriculum Specifically the parents of students in high school are usually at an age where they are significantly more at risk of developing myocardial infarctions Numerous studies have documented that greater than 50 per cent of the deaths occuring from myocardial infarction occur before the patient arrives at the hospital most of them within one hour of onset of acute symptoms [2, 4] To improve this pre hospital phase of myocardial infarction mortality it has been suggested that mobile coronary units be dispatched to the home of patients with symptoms suggestive of a myocardial infarction Such a herculean task requires enormous outlays of capital and a large expenditure of medical manpower [2] One of the most significant factor[s] [in] the pre hospital phase of acute myocardial inf[arc]tion is the time delay in the summoning [of] medical assistance after the onset of sympto[ma]tology [17] If the students were instructed in t[he] signs and symptoms of myocardial infarction th[is] should have a positive influence in reducing t[he] delay in summoning medical assistance for th[e] parents of these students Eventually, [this] knowledge would be beneficial to the stude[nts] themselves when they reach the age at wh[ich] myocardial infarctions are a significant risk f[or] them

Another area in which high schools might b[e] utilized as a resource for health care is i[n] screening programs For the past two years, [our] clinic in conjunction with the local heart associa[tion] has been conducting a hypertension scree[n]ing program in area high schools We have foun[d] that the high school is an ideal place to condu[ct] hypertension screening programs because it give[s] us an opportunity to educate large groups of individuals about the hazards of hypertensio[n] and other cardiovascular risk factors, and a small but significant percentage of students are found to have elevated blood pressures and are referre[d] to existing medical facilities for evaluation of the elevated blood pressures It has been repeatedly emphasized that the goal in hypertension detec[tion] should be the identification of the you[ng] individual with elevated blood pressure Despite the repeated emphasis on the importance of youth in the diagnosis of hypertension, there hav[e] been no concerted efforts to screen young adul[ts] for this known cardiovascular risk factor [1] Even the skeptics of the beneficial effects of antihyper[tensive] therapy who are reluctant to treat hyper[tension] in older individuals, readily emphasize the importance of effective therapy in younge[r] persons [18] What better place could be devised t[o] screen these young individuals for hypertensio[n] than during their high school years? In the past many young men were diagnosed as having signif[icant] risk factors such as hypertension o[r] previously undiagnosed medical problems such a[s] proteinurea, etc, during their physical examina[tion] for induction into the armed services Wit[h] the advent of the volunteer army many individ[uals] will not have this mandatory screenin[g] performed Our local heart association has made [a] recommendation to the Board of Education tha[t] blood pressure measurement should be a routin[e]

mination for high school students along with current requirements for audiometric and n examinations. The implementation of this le screening procedure will have profound ic health consequences upon this significant iovascular risk factor in the community
is concluded that the adolescent age group not now receive adequate instruction in iovascular disease and cardiac risk factors. e persons in their late teens and early twen are developing adult habits and life patterns may alter their longevity it is essential that be properly informed about present day wledge of risk factors such as obesity ciga e smoking lack of exercise cholesterol intake hypertension—i.e the predisposing factors of most common cause of death in the United tes, heart disease Serious consideration uld also be given to the implementation of tine determination of arterial blood pressure igh school students since this asymptomatic order with its known increase in morbidity mortality is (1) easily identified by atrau tic methods and (2) it may be the only portunity to screen for hypertension in an ymptomatic basically healthy population that unlikely to frequent doctors offices or health re facilities

mmary

Current high school health curricula do not equately educate students about the relevant alth problems of the nineteen seventies though cardiovascular disease stroke and ncer account for 70 per cent of the deaths in the nited States high school health curricula garding these topics are conspicuously deficient ediatric cardiologists practice primary preven on and adult cardiologists usually recommend reventative measures to the middle aged popu ation but there has been little emphasis upon isease prevention and identification of risk actors in the adolescent and young adult age roup In addition to teaching physical fitness nd nutrition high school health curricula should ocus attention on known risk factors of the eading causes of morbidity and mortality in the nited States. Screening for readily identifiable disorders such as hypertension should become a routine procedure in high schools and the deter mination of arterial blood pressure should be incorporated into the current testing procedures commonly employed in schools—such as audiom etry and vision testing The structured environ ment of a school curriculum and the capability of todays high school students to comprehend disease states and risk factors suggests that high school students should be the target of intensified and updated health care information programs

REFERENCES

1 Wynder E. L., and Peacock P The practice of disease prevention J.A.M.A 229 1743, 1974
2 Feinleib, M., and Davidov M E. Coronary heart disease mortality A community perspective J.A M.A. 222 1129 1972
3 Hainton C and Peterson H Deaths from coronary heart disease in persons fifty years of age and younger N Engl. J Med 268 569 1963
4 Yoon, I and Watts, R. A mobile coronary care unit An evaluation for its need, Ann. Intern Med 73 61 1970
5 Cooper J Steel, K., and Christodoulou J Mobile coronary care A controversial innovation N Engl J Med 281 906, 1969
6 Soffer A. Only one-third reach the hospital. Dis. Chest 55 272, 1969
7 McNamara, J J Molot M A Stremple J F., et al. Coronary artery disease in combat casualties in Vietnam J.A.M.A. 216 1185 1971
8 Enos, W F Holmes, R. H and Beyer J Coronary disease among United States soldiers killed in action in Korea Preliminary report J.A M.A 152 1090 1953
9 Mitchell, S. C Symposium on Prevention of Atherosclerosis at the Pediatric Level, Am J Cardiol. 31 539 1973
10 McMillan, G. C Development of arteriosclerosis, Am. J Cardiol. 31 542, 1973
11 Levy R. I and Rifkind B M Diagnosis and management of hyperlipoproteinemia in infants and children Am. J Cardiol 31 547 1973
12 Roberts, W C Ferrans, V J Levy R. I., et al. Cardiovascular pathology in hyperlipoproteinemia Am J Cardiol. 31 557 1973
13 Leventhal, H Changing attitudes and habits to reduce risk factors in chronic disease Am J Cardiol. 31 571 1973
14 Schubert, W K Fat nutrition and diet in childhood Am J Cardiol 31 581 1973
15 Mitchell, S C and Jesse M J Risk factors of coronary heart disease—Their genesis and pediatric implications, Am J Cardiol. 31 588, 1973
16 Blumenthal, S Prevention of atherosclerosis, Am J Cardiol. 31 591 1973
17 Yu P N Prehospital care of acute myocardial infarction Circulation 45 189 1972
18 Fry J Natural history of hypertension—A case for selective non treatment, Lancet 2 431 1974

Clinical communications

Heart rate and blood pressure responses during sexual activity in normal males

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Louise Mansfield, R N
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Counseling the cardiac patient, especially following myocardial infarction as to types and extent of physical activity should include specific advice regarding sexual intercourse This subject assumes especial importance where the individual concerned is relatively young and has been sexually active prior to his myocardial infarction Unfortunately there is considerable folklore surrounding sexual activity and its relationship to myocardial infarction and sudden death Recent observations reported by Hellerstein and Friedman[1] have documented the modest rise in maximal heart rate (HR) obtained by middle aged men during sexual intercourse with their wives in the privacy of their homes but the blood pressure (BP) response to sexual activity has not been measured in this setting It has been the opinion of one of the authors that sexual intercourse carried out with the male on top (MOT) position would be more stressful as compared to the male on bottom (MOB) position because of the necessity of the male to support himself with his arms above his female partner[2] This form of isometric arm exercise might be expected to cause a greater increase in BP as compared to intercourse performed in the MOB position This study was designed to evaluate the cardiovascular stress of normal males during sexual intercourse in two positions

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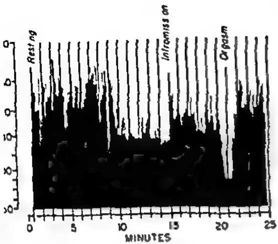
Material and methods

Ten male subjects, including five physicia one physiologist three paramedics and one lab ratory technician, ranging from 24 to 40 years age (mean 29 3 years), volunteered to participa in the study Each participant was asked t monitor himself during episodes of sexual inte course with his wife in the privacy of his home The electrocardiogram (ECG) was corded with a portable ECG tape recorder (Holte Electrocardiocorder, Model 350) The electrod were attached to the chest to obtain a modifie Lead II record at least 1 hour prior to th initiation of sexual activity The arm BP recorded with an automatic cuff inflating devi which utilizes an ultrasonic doppler device t detect systolic and diastolic BP (Roche Arten osonde Model 1260) With careful instruction accurate BP free of artifact was obtained with this device The beginning of sexual activity wa signaled by a brief disconnect of the ECG elec trodes from the recorder and a careful diary was kept utilizing a bedside clock to identify the time of events The subject was instructed to measure his BP at rest intromission orgasm and at 30 60, and 120 seconds following orgasm

The subject was requested to monitor himself during five episodes of sexual intercourse over a 1 week period the first to orient his wife and himself to the recording equipment and four episodes alternately in the MOT and MOB position Obtaining this data generally required 10 to 14 days Adequate information was obtained during 35 episodes of sexual activity in eight of the 10 original subjects There was no observable difference in HR and BP responses with the first and



1 This figure displays a histogram of R R intervals rded in a subject during sexual intercourse in the MOT tion. The HR is indicated by the log scale in the left. The increased to 94 b p.m during intromission reached a imum of 117 b p.m during orgasm and then decreased dly to ▪ b p.m. at 1?0 seconds following orgasm

bsequent episodes of sexual activity so this riod was included in the data analysis

The ECG s were analyzed for arrhythmia and her abnormalities on a high speed scanner vionics Composite ECG Scanner) HR was dis ayed as a histogram of the RR intervals with ne and related to the diary of events BP adings were then compared with the appro iate HR and the pressure rate product

$$(\text{PRP} = \frac{\text{Systolic pressure} \times \text{HR}}{100})$$

as calculated The data were subjected to anal is of variance in relation to position during xual activity

esults

Continuous HR and intermittent BP moni oring was carried out on ten subjects Variable ata were obtained in eight male subjects during 5 episodes of sexual intercourse 16 in the MOT osition and 19 in the MOB position An example f the HR response during intercourse is shown in ig 1 and the HR data for all the patients are ummarized in Fig ▪ and Table I In the MOT osition resting HR was 60 ± 8 increased to 92 ± 13 at intromission and was maximal at orgasm at 114 ± 14 HR fell rapidly to 69 ± 12 at 120 seconds following orgasm Similar HR responses were recorded for the MOB position

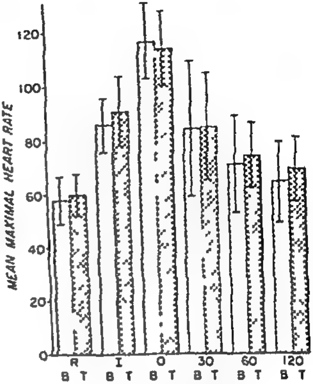


Fig 2 This figure represents the mean ± 1 S D HR response during rest (*R*) intromission (*I*) orgasm (*O*) and 30 60 and 120 seconds following orgasm. The stippled bars represent the MOB position and the cross-hatched bars the MOT position.

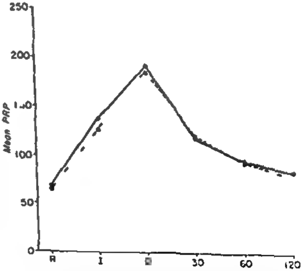


Fig 3 This graph represents the mean PRP during each phase of sexual intercourse in eight subjects. The solid line represents the PRP for the MOT position and the dashed line the MOB position.

Table I Summary of patient data

	Rest	Intromission	Orgasm	30 sec	60 sec	120 sec
Heart rate						
MOT	60 ± 8	92 ± 13	114 ± 14	85 ± 20	74 ± 12	69 [illegible]
MOB	58 ± [illegible]	86 ± 10	117 ± 14	84 ± 2[illegible]	71 ± 18	64 [illegible]
Systolic BP						
MOT	112 ± 8	118 ± 12	163 ± 11	13[illegible] ± 8	128 ± 8	118 [illegible]
MOB	113 ± 5	143 ± 20	161 ± 18	140 ± 13	1[illegible]9 ± 9	1[illegible] [illegible]
Diastolic BP						
MOT	66 ± 8	79 ± 13	81 ± 17	75 ± 12	[illegible]0 ± 9	69 [illegible]
MOB	70 ± 7	74 ± 10	77 ± 12	71 ± 12	71 ± 6	[illegible] 6
Pressure rate product						
MOT	67 ± 11	136 ± 16	169 ± 34	117 ± 35	94 ± 19	8[illegible] [illegible]
MOB	6[illegible] ± 12	12[illegible] ± 27	183 ± 31	118 ± 48	93 ± [illegible]8	77 [illegible]

with the maximal HR at orgasm being 117 ± 14 No significant difference in HR occurred comparing the two positions

BP showed a similar response to HR during sexual activity in the MOT position with a mean resting BP of 112/66 increasing at intromission to 118/79 attaining a maximum of 163/81 at orgasm and returning to near resting level of 118/69 by 120 seconds following orgasm (Table I) The BP tended to be slightly lower in the MOB position during intromission and was similar during other phases of intercourse and recovery The PRP showed no significant difference in the two positions of intercourse (Fig 3)

There were few changes in the ECG during sexual activity noted in these normal subjects One subject had repeated premature atrial contractions and another had changes in P wave configuration during orgasm There were no changes in the QRS, ST segment or T wave observed in any subject

Discussion

There is little relevant information available describing the HR and BP responses to sexual intercourse in a home setting free from observers or complex monitoring equipment Earlier studies carried out in artificial settings indicated that HR and BP were maximal during orgasm with HR increasing up to the 140 to 180 range whereas BP increased to more than 200 systolic in many subjects[3,5] More useful information comes from studies of Hellerstein and Friedman[1] who reported ECG information obtained during sexual intercourse on 14 middle aged men (average, 47 5 years) with ischemic heart disease [illegible] Astrand s[6] published data on maximal H[illegible] achieved with upright exercise by age group [illegible] mean maximal HR of 114 achieved by our [illegible] subjects represents 61 per cent of the maxima[illegible] HR for the 20 to 29 year old age group Th[illegible] maximum HR of 117 obtained by Hellerstein a[illegible] Friedman in ischemic heart disease patients is [illegible] per cent of maximal HR predicted for age ran[illegible] 40 to 49 years

It must be remembered, however, that patie[illegible] with ischemic heart disease have reduced max[illegible] mal HR as compared to normals of similar a[illegible] Bruce and associates[1] have reported HR data during maximal treadmill exercise on a large group of men including 2 094 normal subjects and 1 057 men with ischemic heart disease The normal men (mean age, 44 5 years) had a maximal HR of 181 ± 12 whereas 249 men (mean a[illegible] 50 4) with a prior myocardial infarction had a maximal HR of 156 ± 20 Those 495 patients with angina and prior myocardial infarction had even lower maximal HR s of 115 ± 23 during maxi[illegible] mum exercise If we compare Hellerstein and Friedman s patients with those reported by Bruce and associates with prior myocardial infarction a mean HR of 117 at orgasm represents 75 per cent of their predicted maximum If these individuals also had angina pectoris we would predict that a HR of 117 is 81 per cent of maximum

There are no other comparable reports of BP measured during sexual intercourse in the uncontrived home setting The mean maximum BP of 163/81 during orgasm is less than has been usually reported[3,5] Hellerstein and Friedman in

attempt to predict BP during orgasm studied ır cardiac patients at a later time during cle exercise to the same HR achieved during asm and measured arm BP The results of ır study are similar to ours with a mean ximum BP of 162/89 The higher diastolic BP y be accounted for by variations in age hand o response to bicycle exercise or other factors

responses of coronary and hypertensive pa nts during sexual activity may differ from ponse in normals and should be evaluated

The results of this study failed to confirm the liefs of some cardiologists that the apparently ore restful MOB position during sexual inter results in less increase in HR and BP and is erefore preferable for the cardiac patient This ıdy also confirms the observations of Heller ın and Friedman that cardiac work associated ı th sexual intercourse is of moderate intensity ıd may represent 80 per cent of maximum for ıe post-myocardial infarction or angina patient he ability of the cardiac patient to tolerate this ıvel of cardiac work can be evaluated by exer sing the patient to a HR of 115 under supervised esting conditions This HR is usually achieved n completion of Stage I of the Bruce Exercise est

The physician who is counseling the cardiac atient must remember that the cardiovascular esponses described here were recorded while men ere having sexual relations with their wives of at east 6 months duration Sexual activity with a new or unfamiliar partner especially when it occurs in strange surroundings or following heavy ood or alcohol intake may result in higher HR and BP responses detrimental to the cardiac pa tent This is suggested by frequent reports of sudden death during coitus in a hotel setting when the female partner is not the spouse Sudden death or myocardial infarction during sexual intercourse is rarely reported in women

In patients with ischemic heart disease and exercise induced arrythmias ECG monitoring during sexual activity may yield important infor mation Further studies of the ECG response to sexual activity in cardiac patients especially following myocardial infarction are needed

Summary

In order to properly advise cardiac patients in the regulation of their sexual activity more basic physiologic information is needed concerning the cardiovascular effects of sexual intercourse This study examined the effects of the male s position during sexual intercourse on heart rate and blood pressure responses Eight men 24 to 40 years of age were studied in the privacy of the bedroom during sexual activity with their wives The ECG was monitored continuously by portable tape recorder and the arm blood pressure (BP) was measured intermittently with an automatically inflated cuff and ultrasonic detector device controlled by the subject A total of 35 episodes of sexual intercourse were monitored 16 were with the male-on top (MOT) and 19 were in the male on bottom (MOB) position The mean maximal heart rate (HR) for MOT at orgasm was 114 com pared to 117 in the MOB position representing 61 per cent of predicted maximal HR for men in the 20 to 29 age group Mean BP at orgasm in the MOT was 163/81 and 161/77 in the MOB posi tion The differences in mean HR BP and pres sure rate product (PRP) were not statistically significant with regard to position at rest intro mission orgasm or during the recovery period

This study indicates no difference in the heart rate and BP responses of the male during sexual intercourse in two different positions. There is therefore no physiologic basis for advising cardiac patients to utilize the MOB position during sexual intercourse

REFERENCES

1 Hellerstein H K and Friedman E H Sexual activity and the post coronary patient Arch. Inter Med. 125 98 19 0
2. Koller R. Kennedy J W Butler J C et al Coun seling the coronary patient on sexual activity Postgrad Med 51 133, 197_
3 Masters, W H and Johnson V E Human sexual response Boston 1966, Little Brown & Company
4 Boas, E P and Goldschmidt E F The heart rate Springfield Ill. 193? Charles C Thomas, Publisher
5 Bartlett R J Jr Physiologic responses during coitus, J Appl. Physiol. 9 469 1956
6. Astrand, I Aerobic work capacity in men and women with special reference to age Acta Physiol Scand 49(Suppl. 169) 1960
7 Bruce R.A. Fisher L.D Cooper M N and Gey G O Separation of effects of cardiovascular disease and age on ventricular function with maximal exercise Am J Cardiol 34 57 1974
8. Ueno M The so-called coition death Jap J Legal Med 17 333 1963

Conduction disturbances after total correction of tetralogy of Fallot

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The electrocardiographic (ECG) changes produced at surgery in all patients undergoing total correction of tetralogy of Fallot at the Hospital for Sick Children, Toronto, from 1955 through 1974 were reviewed Particular attention was directed to the presence of postoperative right bundle branch block combined with left anterior hemiblock because a recent report indicated a 25 per cent late mortality rate in children with this ECG pattern[1] Data from our institution and others have indicated that the prognosis with this lesion may be better than first reported[2,4]

Methods

The ECG's of all late survivors (over 30 days) of total correction of tetralogy of Fallot were reviewed There were 506 such operations through Dec 31, 1974, with 437 late survivors (86 per cent) We have excluded from the study 11 patients who had left axis deviation, one patient who had the sick sinus syndrome, and one patient with the Wolfe Parkinson White syndrome preoperatively The remaining 424 were in normal sinus rhythm with normal PR interval and had right axis deviation preoperatively

Right bundle branch block (RBBB) was present when there was a QRS complex exceeding 120 msec with a right terminal vector Right bundle branch block combined with left anterior hemiblock (RBBB LAH) was diagnosed when criteria of Rosenbaum were met (1) the [illegible] QRS forces superiorly and to the left in frontal plain, (2) the initial QRS (first 20 msec) inferiorly and to the right, and (3) the late QRS forces (last 40 msec) primarily to the right Different groups have defined left anterior hemiblock in the presence of right bundle branch block as an axis of 240 to 300 degrees,[1,6] less than 330 degrees[7,8] and less than 360 degrees[2,3] We have continued to define it as 240 to 360 degrees in the population of corrected tetralogy of Fallot because all of these children have had an acute leftward shift in axis of at least 90 degrees simultaneous with the appearance of right bundle branch block, to an axis which is leftward of the accepted normal for children[9] We know no electrophysiological method short of intracardiac mapping to confirm RBBB LAH as patients with this ECG may have either normal or abnormal His bundle electrograms[2,7]

Results

Of the 424 patients 404 were alive at the conclusion of the study The ECG of these shows that 91 (23 per cent) have RBBB LAH (Table I) However, only 54 (13 per cent) have an axis between 240 and 300 degrees This may reconcile some of the apparent discrepancy in the frequency of production of RBBB LAH in different series

Late deaths There have been 20 late deaths in this series Fifteen were attributable to nondysrhythmic causes five deaths after reoperation, four from prolonged hospital infections, three

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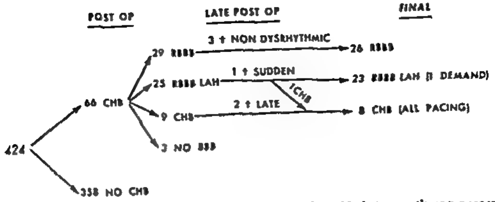


Fig 1 Flow chart of the 66 patients with postoperative complete heart block, transiently or permanently

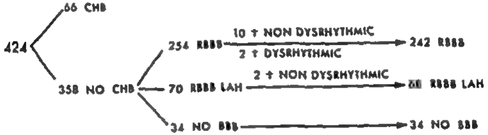


Fig 2. Flow chart of the 358 patients with no history of postoperative complete heart block.

rom congestive cardiac failure two from infective endocarditis and one death from pulmonary vascular disease There have been five apparent dysrhythmic deaths. Although there are nine late survivors who have premature ventricular contractions on their resting ECG s none of these five apparent dysrhythmic deaths occurred in a patient with documented premature ventricular contractions. Two patients who developed *complete heart block (CHB) at the time of correction* died 33 and 86 days postoperatively without ever having reverted to sinus rhythm or having been discharged from the hospital One patient with RBBB-LAH and a history of postoperative CHB died suddenly 8½ months postoperatively One patient who had not had postoperative conduction problems in hospital began to have syncopal attacks 29 days after correction He went into intermittent heart block for several months but advanced to irreversible CHB 3½ months postoperatively He was managed without a pacemaker until dying suddenly 27 months after surgery He had RBBB with an axis of 105 degrees prior to the development of CHB Finally one patient without postoperative CHB who had a history of blackouts with one documented episode of supraventricular tachycardia 4 years after correction but who was on no therapy and had RBBB with an axis of 135 degrees on ECG was found dead in bed 6 years postoperatively Thorough pathological examination with special attention to the conduction system was performed but no evidence of interruption of the A V node His bundle or left or right bundle branches was observed

Table I The current ECG of the 404 survivors with preoperative sinus rhythm normal PR interval and right axis deviation

268	RBBB
91	RBBB + LAH (27%)
37	NO BBB
8	CHB
404	

Postoperative complete heart block Sixty six of these 424 late survivors had postoperative CHB nine permanently and 57 transiently (Fig 1) Of the nine patients with *persistent CHB* two died late in hospital and seven continue in CHB 1 to 12 years postoperatively Five of these seven had permanent pacemakers placed shortly after total correction while the other two who

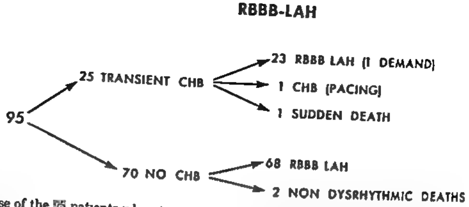
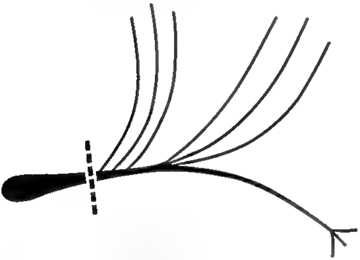


Fig 3 The course of the 95 patients who at some time after correction have had RBBB LAH Those without a history of transient complete heart block have had no dysrhythmic morbidity or death to date



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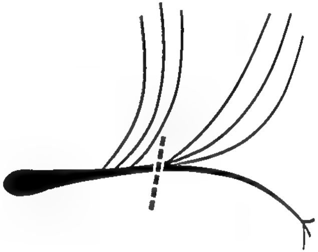

Fig 5 More distal injury to the specialized A V conduction system where the right bundle branch and left anterior fascicle are injured simultaneously

went home in CHB have had permanent pacemakers placed 7 and 12 years after surgery subsequent to Stokes Adams attacks We currently have no patients in CHB without permanent pacemakers

Of the 57 patients who had transient CHB 29 left the hospital with RBBB 25 with RBBB LAH, and three without bundle branch block Of those with RBBB LAH, three have had morbid events—one sudden death, one reversion to CHB 13 months postoperatively and one patient with recurrent syncope who has had a permanent demand pacemaker inserted Of those with RBBB only, there have been three deaths after reoperation but no significant rhythm disturbances

Late survivors without early postoperative complete heart block There are 358 late survivors who have no history of postoperative CHB (Fig 2) Two have died dysrhythmic deaths (see above) but none of the others has developed intermittent or complete heart block There were 70 patients with RBBB LAH in this group Two have died nondysrhythmic deaths The other 68 have been followed for 294 patient years the longest follow up being 14 years, without any dysrhythmic morbidity or death Fifty nine of the 68 have either been seen by us in the last 2 years of the study or responded to a questionnaire concerning their condition at the conclusion of the study Nine have been lost to follow up

Thus 12 of the 66 patients who had postoperative CHB have suffered dysrhythmic morbidity or death three have died eight are in CHB with pacemakers and one with RBBB LAH has a demand pacemaker for syncope Only two of the 358 patients without postoperative CHB have suf

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The anatomy of the atrioventricular conduc n system in tetralogy of Fallot as described by v [3] and recently confirmed during surgery by rongrad and his associates, [11] makes it espe lly vulnerable to injury during operative re- ir Pathological studies have confirmed that ch injury occurs. [4] When there has been post erative CHB it is logical to assume that there s been injury to the A V node to the His undle centrally (Fig 4) or to the three divisions f the conducting system more peripherally Pe pheral injury could occur to each fascicle indi idually or to combinations of fascicles as they ourse together through the specialized A V onduction system Though these patients may eturn to sinus rhythm some clearly have esidual trifascicular disease with prolonged H V ntervals. Narula and Samet[7] stated that an abnormal H V time in patients with RBBB and LAD is indicative of disease elsewhere in the His Purkinje system in addition to the right bundle branch and the anterior division of the left bundle Furthermore injury in one area of the specialized conduction system does not rule out damage elsewhere It has been demonstrated that RBBB can be produced by right ventriculotomy alone and it is probable that patients with a history of postoperative CHB who subsequently have RBBB only on ECG have had only tran sient damage to the proximal conducting system

Significantly the left anterior and right bundles frequently run together below the ventricular septal defect in tetralogy of Fallot after the left posterior division has been given off[11] Patients who have had total correction of tetralogy of Fallot without a history of complete heart block, but who show RBBB LAH on their ECG may have had injury in this area during closure of the VSD without any injury to the left posterior bundle (Fig 5) They would therefore remain in sinus rhythm postoperatively but have a continuing ECG pattern of RBBB LAH

Although the final outcome of this large group of patients with RBBB LAH without any history of postoperative CHB will be known only with time their course to date would indicate that the left posterior fascicle has been spared during surgery For the period of the study they have had no late CHB or sudden death However the smaller group of patients with RBBB LAH and a history of transient postoperative CHB have had significant morbidity They should be carefully followed and evaluated for trifascicular disease by His bundle electrograms and atrial pacing to measure the refractory period of the A V node It is conceivable that at some time in the future we may insert demand pacemakers into asympto matic postoperative patients who have docu mented trifascicular disease although we are currently not doing this.

REFERENCES

1 Wolff G S., Rowland, T W., and Ellison R. C Surgically induced right bundle branch block with left anterior hemiblock Circulation 46 587 1972.

2 Godman, M J., Roberts, N K and Izukawa, T Late postoperative conduction disturbances after repair of ventricular septal defect and tetralogy of Fallot Circula tion 49 214 1974

3 Downing, J W Kaplan S and Bove K F Postsur gical left anterior hemiblock and right bundle branch block, Br Heart J 34 263 1972

4 Steeg, C N Krongrad, E., Davachi, F Bowman, F O Malm, J R., and Gersony W M Postoperative left anterior hemiblock and right bundle branch block following repair of tetralogy of Fallot Circulation 51 1026, 1975

5 Rosenbaum, M B Corrado G., Oliveri, R., Castellanos, A and Elizari, M V Right bundle branch block with left anterior hemiblock surgically induced in tetralogy of Fallot, Am. J Cardiol. 26 12 1970

6 Rosenbaum, M B The hemiblocks Diagnostic criteria and clinical significance Mod Concepts Cardiovasc Dis 39 141 1970

7 Narula, O S., and Samet P Right bundle branch block with normal, left or right axis deviation Am J Med 51 432, 1971

8 Chesler E., Beck, E and Schrire V Left anterior hemiblock and right bundle branch block before and after surgical repair of tetralogy of Fallot, Am Heart J 84 45 1972

9 Moss, A. J., and Emmanouilides, G C Practical pedi atric electrocardiography Philadelphia and Toronto 1973 J B Lippincott Co pp 28-31

10 James, F W and Kaplan S Sudden unexpected cardiac arrest in patients after surgical correction for tetralogy of Fallot, Am J Cardiol 35 146 1975 (abst.)

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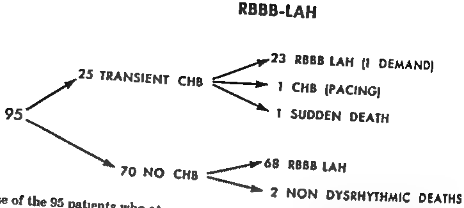

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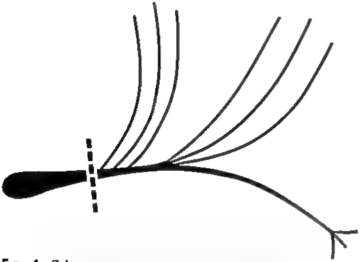

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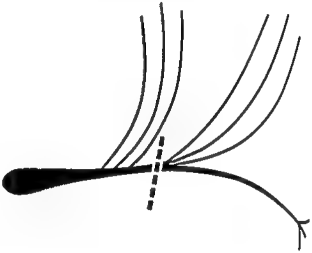

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4 Steeg, C N Krongrad E Davachi F., Bowman F O Malm, J R. and Gersony W M Postoperative left anterior hemiblock and right bundle branch block following repair of tetralogy of Fallot, Circulation 51 1026 1975.
5. Rosenbaum, M B., Corrado G Oliveri, R Castellanos A., and Elizari, M V Right bundle branch block with left anterior hemiblock surgically induced in tetralogy of Fallot, Am. J Cardiol. 26 12, 19 0
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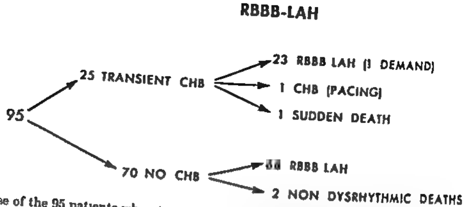

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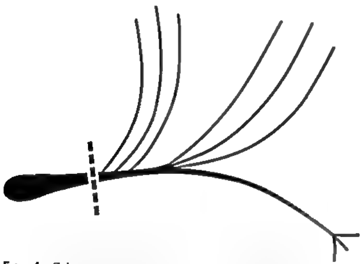

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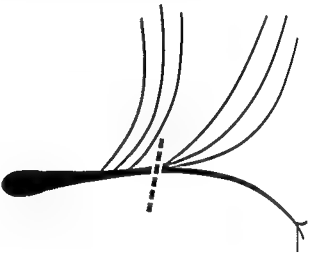

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ects of treadmill exercise on the timing of the heart and arterial sounds, and the slope of the brachial arterial pulse wave

shiaki Inagaki M D
ndel Wassermil M D **
aon Rodbard M D Ph D †
arte Calif

ercise has been widely utilized to test the ponse of the myocardium to increased work ads as measured by the effects on heart rate anges in rhythm and electrocardiogram CG) Recently the treadmill has been used in ich exercise stresses Heart rate systolic pres ure and cardiac output increase in accord with he severity of the exercise

We have utilized the noninvasive method of phygmorecording (pulse recording) to analyze he effects of exercise stress on the cardiovascular ystem This technique uses electronic instrumen ation to align time and record the onsets and lurations of the heart and arterial sounds in a equence of heart beats As a cuff on the arm is leflated a photographic recording is generated providing a calibrated contour of the upstroke of the brachial arterial pressure wave timed with respect to the onset of the cardiac cycle [2] Infor mation of this type aids in the analysis of the cardiovascular responses to exercise stress The present study presents data on normal subjects

Materials and methods

Sixteen subjects 18 to 61 years of age were studied These subjects were asymptomatic and had no history of cardiac or thyroid disease Measurements were obtained with a sphygmore corder shown schematically in Fig 1 Heart and arterial sounds were recorded as the subject rested supine on a comfortable examining table

With each beat, the onset of the QRS complex of Lead I of the ECG triggered the sweep of the beam of a cathode ray oscilloscope

A sphygmomanometer cuff on the upper arm was inflated to approximately 200 mm Hg and then deflated at about 3 mm Hg per second The vertical position of the oscilloscope beam cali brated in millimeters of mercury was linearly related to the pressure in the cuff

The arterial sounds of Korotkoff and the heart sounds were simultaneously recorded on the oscil loscope A crystal microphone over the brachial artery introduced the arterial Korotkoff sounds into amplifiers, filters, and the intensity modula tion (Z axis) circuit of the scope The signals from a second microphone over selected sites on the anterior thorax were simultaneously amplified filtered and introduced into the Z axis circuit This arrangement rendered the beam invisible except during the input of acoustic signals (a "positive deflection toward the microphone) Further details of the automated method have been described [2,3] This procedure provides an objective permanent record of the arterial pres sure wave contour blood pressure the intervals between onsets of the QRS complex and the Korotkoff sounds at systolic and diastolic pres sure (QK QK$_4$) and the slope (dP/dt) of the foot (lower 20 mm Hg) of the pressure wave QS, QS, S S$_2$ and other cardiac time intervals This method has been validated by comparison with direct intra arterial pressure recordings

Treadmill exercise was performed for 4 minutes

From the Di isi n f Card ol City of H pe Med cal Center

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patients with tetralogy of Fallot A follow up study of 251 patients for an average of twelve years, Am J Cardiol 35 164 1975 (abst)

12. Izukawa, T Clarke M., and Trusler G A Late complete trifascicular heart block resulting from cardiac surgery Circulation 44(Suppl. II) 181 1971

13 Lev M The architecture of the conduction system in congenital heart disease II Tetralogy of Fallot Arch Pathol. 67 572 1959

14 Krongrad E Malm J R Bowman F O Hoffman B F Kaiser G A and Waldo A L. Electrophysiological delineation of the specialized atrioventricular conduction system in patients with congenital heart disease I Delineation of the His bundle proximal to the membranous septum J Thorac. Cardiovasc. Surg 67 875 1974

15 Krongrad E Malm J R. Bowman F O Hoffman B F., and Waldo A. L. Electrophysiol of the specialized A V conduction system in patients congenital heart disease, II Delineation of the bundle and the right bundle branch, Circulation 49 1974

16. Lev M, Fell E H Arcilla R and Weinberg M Surgical injury to the conduction system in ve septal defect, Am. J Cardiol. 14 464 1964

17 Anderson P A. W., Rogers, M C Canent R Jarmakani, J M M Jewett, P H and Spach M Reversible complete heart block following o surgery Circulation 46 514 1972.

18. Gelband, H Waldo A L. Kaiser G A Bowman F Malm J R., and Hoffman, B F Etiology of bundle-branch block in patients undergoing total correction of tetralogy of Fallot, Circulation 44 1022, 1971

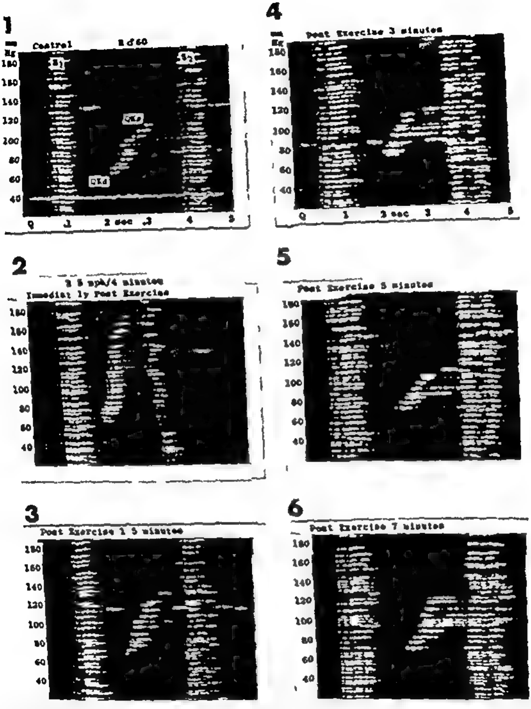

Fig 2 *(1)* Control recording in a 60-year-old man. S begins at 60 msec. S at 400 msec BP 115/65 QK is 210 msec. QK, is 300 msec. *(2)* After treadmill exercise S begins with a brief faint sound at 40 msec Systolic pressure is 180 mm Hg with a QK, of 270 msec. diastolic pressure is 65 mm Hg with a QK of 150 msec At the beginning of this recording (top) the second QS is .50 msec but this progressively increases to 300 msec (bottom) heart rate slows *(3)* At 1 5 min. following exercise S appears at 50 msec the second heart sound is at 330 msec QK is 2"0 and QK, is 180 msec *(4 5 6)* Taken at 3 5 and 7 minutes respectively following the end of exercise The tracings approach control values The second sound exhibits physiological splitting varying with respiration The long duration of the Korotkoff sounds in prints *4 5* and *6* correlates with increased blood flow through the vascular bed of the forearm and hand

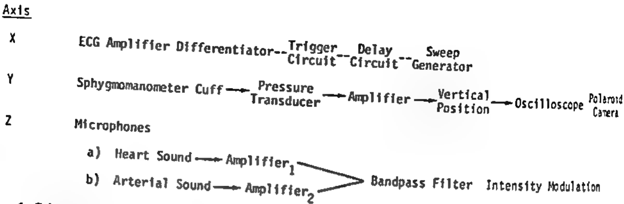

Fig 1 Schematic flow diagram of sphygmorecorder for simultaneous analysis of heart and arterial sounds Discussed in text

Table I Values of parameters before and at various intervals after treadmill exercise expressed as per cent of control values (means and standard deviations)

	Control value	% of control value minutes after exercise			
		0	*1 5*	*3*	*5*
HR	76	146	120	115	110
	± 14	34	19	17	14
RR (msec)	802	72	8.	89	92
	165	13	13	12	10
P (mm Hg)	120	126	113	104	100
	16	10	12	11	7
P_d (mm Hg)	73	99	97	97	102
	10	10	10	14	14
P P (mm Hg)	47	170	141	116	103
	11	29	37	25	28
QK (msec)	311	76	86	90	97
	53	20	12	14	16
QK_d (msec)	205	71	85	91	98
	13	15	11	12	10
QK QK_d (msec)	106	79	90	93	106
	52	29	27	36	37
Slope dP/dt	0 59	220	199	140	122
(mm Hg/msec)	0 22	72	.9	60	44
QS (msec)	48	86	93	97	102
	4	10	12	13	14
QS_2 (msec)	362	80	89	92	96
	[illegible]	[illegible]	8	7	6
S S_2	314	79	[illegible]	93	97
	26	7	6	8	8

at 2 5 miles per hour (4 0 km per hour) at a grade of 10 per cent Recordings on Polaroid prints were taken at rest prior to exercise, immediately after exercise, and at 1 5, 3, 5 and 7 minutes following exercise

Results were analyzed by Student s paired t test, and by correlation and regression me Changes in parameters (e g HR, BP QK_d) we analyzed within each subject to elimin between subject variability in baseline measu ments Similar conclusions were obtained w er one used an absolute or relative (per c change from control measurements

Results

Representative sphygmorecordings from normal subject are shown in Fig 2

Mean values and standard deviations of seve indices of cardiac function before and at vario intervals after treadmill exercise are given Table I The standard errors of the mean (S E M would be only 0 25 times the standard deviatio Results are summarized in Fig 3

Heart rate At rest, the heart rate ranged fro 48 to 104 beats per minute Following the exercise the mean heart rate increased to 146 ± 34 pe cent above the resting level, returned approx mately half way to the control rate in 2 minutes and nearly completely (to 110 per cent of control within 5 minutes Results were expressed as pe cent of control for each subject, to permit ana ysis within subject and to facilitate compar ison between the various indices of cardiac fun tion Changes in the reciprocal of HR, the interval convey the same information

Systolic pressure (P_s) The systolic pressure rest averaged 120 ± 16 mm Hg Immediatel after exercise P had increased an average of mm Hg (26 per cent) and it then fell progressive to the control value within about 5 minutes for a subjects

Diastolic pressure (P_d) The average diastolic pressure 73 ± 10 mm Hg prior to exercise wa affected only slightly during the 5 minute interva of observation following the exercise In individ

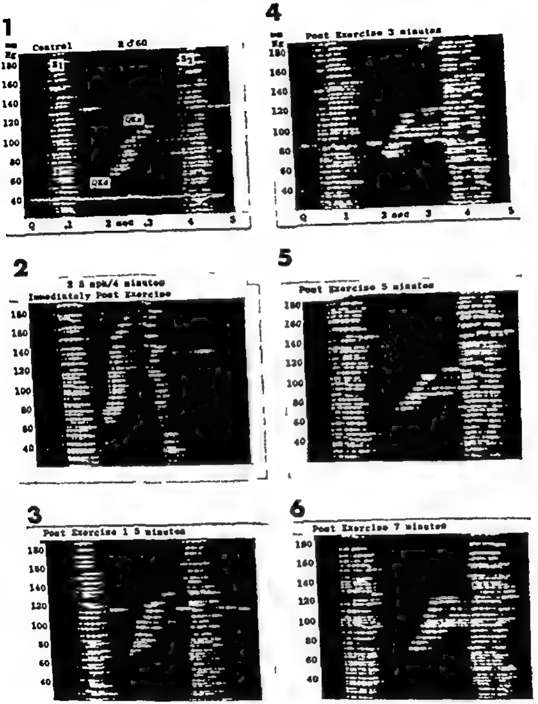

Fig 2 *(1)* Control recording in a 60-year old man S begins at 60 msec. S at 400 msec. BP 115/65 QK is 210 msec., QK_4 is 300 msec *(2)* After treadmill exercise S begins with a brief faint sound at 40 msec. Systolic pressure is 180 mm. Hg with a QK of 2/0 msec. diastolic pressure is 65 mm Hg with a QK of 150 msec At the beginning of this recording (top) the second QS is 250 msec but this progressively increases to 300 msec (bottom) as heart rate slows. *(3)* At 1.5 min following exercise S appears at 50 msec the second heart sound is at 330 msec QK is 2"0 and QK_4 is 180 msec *(4 5 6)* Taken at 3 5 and 7 minutes respectively following the end of exercise The tracings approach control values. The second sound exhibits physiological splitting varying with respiration. The long duration of the Korotkoff sounds in prints *4 5* and *6* correlates with increased blood flow through the vascular bed of the forearm and hand.

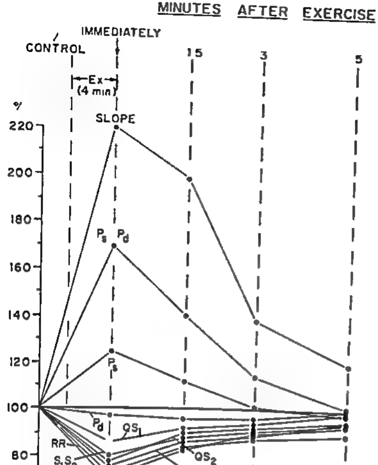

Fig 3 Summary of changes in cardiac parameters after treadmill exercise The percent changes from control (resting) values in the several parameters mentioned are shown immediately after exercise and at 1 5 3 and 5 minutes post exercise

Table II Correlation and regression analysis for selected pairs of variables

Variables x	Variables y	Slope	r
QS	RR	1 09 ± 0 15	0 73
S S	RR	0 98 ± 0 14	0 74
RR	QK_d	0 75 ± 0 10	0 72
S_1S	QK_d	0 96 ± 0 10	0 80
P P_d	QK_d	−0 27 ± 0 03	−0 69
dP/dt	QK_d	−0 093 ± 0 03	−0 42

uals with diastolic pressures below 80 mm Hg, it tended to fall 5 to 10 mm Hg in the observations immediately following exercise Most of our subjects with diastolic pressures above 80 mm Hg exhibited a rise of about 10 mm Hg immediately following the exercise

Pulse pressure (P_s P_d) Inasmuch as diastolic pressure was virtually unaffected by the exer the pulse pressure increased directly with systolic pressure The mean resting pulse press of 47 ± 11 mm Hg increased to an average of immediately after exercise and returned normal values within 5 minutes

QK This is the interval from the onset electrical depolarization (Q) to the onset of t arterial Korotkoff sound (K) The QK inter longest at systolic pressure and shortens as t cuff pressure falls to the diastolic pressure

QK_s This time interval, from Q to the onset the arterial Korotkoff sounds at systolic (s) sure averaged 311 ± 53 msec Immediately af the treadmill exercise, it had decreased by 9 p cent and it returned to resting values in 3 to minutes

QK_d As the cuff pressure fell in each test, th onsets of the Korotkoff sounds appeared progressively earlier in the cardiac cycle In restin normal subjects, the onset of the final sound o the Korotkoff series marked the diastolic cu pressure At rest, the average value for this QK interval was 205 ± 13 msec Immediately following the exercise, this interval had shortened by 6 msec (29 per cent) to an average of 145 msec Recovery toward the control value was rapid. I 1 5 minutes QK_d was approximately halfway ba to the initial value In 16 of 18 subjects, QK_d returned to within 10 per cent of the control val by 5 minutes

QK_s QK_d This arterial pressure rise time interval was affected to a minor and quite variable extent by exercise The average resting QK_s QK_d in the present subjects was 106 ± 52 msec and it changed to 79 ± 29 per cent of contr following exercise

Slope (dP/dt) When the subject was at rest the slope of the first 20 mm Hg of the arterial pressure upstroke averaged about 0 59 mm Hg msec Immediately after the exercise, the average slope had more than doubled (range, 136 to 4 per cent) and it returned to within 10 per cent o control values in 16 of 18 subjects within minutes

QS_1 In normal subjects the time interval from the Q wave trigger to the onset of the first heart sound S_1 was 48 ± 4 msec Immediately after exercise the mean QS_1 interval was found to shortened about 6 msec QS_1 returned to n in 5 to 7 minutes in all subjects

QS_2 The interval between the onset of Q to onset of S_2 averaged 362 ± 28 msec in norm

g subjects. Immediately following the exer the mean QS_2 interval was shortened to 287 ± 27 msec. and it returned to normal s within 5 minutes in all subjects.

$_2$ or QS_2 minus QS_1. At rest the interval the onsets of the first and second heart ls was 314 ± [illegible] msec Immediately after the ise S_1S_2 was shortened by a mean of 21 per The resting value was regained in 5 minutes pattern of rapid recovery of the timing of QS_1) was documented in the beat to beat re ings obtained during the first minute or two ediately following the exercise (e g Fig 2)

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ne correlation coefficients of several pairs of imeters were computed As shown in Table II vs. QS_2, RR vs S_1S_2, RR vs. QK_4 and QK_4 vs. correlation coefficients were greater than QK_4 showed a significant—though small correlation with slope

S_2 vs heart rate As heart rate increased owing exercise the interval QS_2 also de ised This relationship was compatible with results of Weissler and associates,[7] Spodick l Quarry Pigott[8] and of Maher and asso tes.

RR The duration of the cardiac cycle (RR erval) shortened with exercise and returned to itrol values with rest The interval QS_2 showed ignificant linear correlation with RR although ignificant departure from linearity was present. R vs S_1S_2 showed a similar nonlinear relation ip QK_4 was not significantly correlated with

In addition to the well documented effects of ercise such as increases in heart rate and pulse essure the sphygmorecorder showed that in ie postexercise period the arterial pulse wave is eeper and arrives at the brachial artery earlier ian when the subject is at rest This early arrival ime was associated with shortened RR intervals nd with somewhat earlier onsets of both S_1 and as well as shortened S_1 to S_2 duration However the shortened QK_4 interval is not en irely due to change in heart rate per se a similar change was seen in a patient with an implanted pacemaker and fixed heart rate

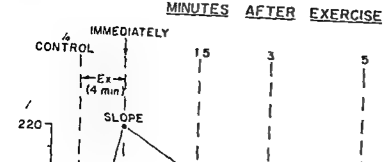
Discussion

The sphygmorecording technique provides an innocuous noninvasive means for noninvasive beat to beat on line recording of the rate of return of the heart sounds, arterial sounds, and pulse wave contour to the resting values. Sphyg morecordings also clearly define the changes in arterial pressure that follow such exertion by an objective means that provides a permanent record[1-4] The changes in HR, P P, and P P_4 following exercise are well documented Results on these variables have been included here to facilitate comparison with other studies, and because of the emphasis on the rate of return of these parameters to normal. The changes in QS_1, QS_2 and S_1S_2 and the systolic time intervals have also been documented previously[7-10] The present results for these variables and for the correlations between HR (or RR) and QS_1 or HR and QS_2 are compatible with these previous studies.

The present study provides new data on several additional parameters of cardiac function QK_4, QK, QK QK_4 and dP/dt of the brachial arterial pulse wave as well as the complete calibrated contour of the upstroke of the pressure wave (Fig 2)

The QK_4 and the slope (dP/dt) are especially sensitive to changes following exercise It should be emphasized that this dP/dt applies only to the brachial artery and is *not* a measure of ventricu lar aortic, or subclavian dP/dt.[11] The changes in QK_4 observed during exercise are due to two main effects (1) shortening of the pre-ejection period PEP[7, 11] and (2) shortening of pulse *transmission* time PTT as previously documented by Kroeker and Wood.[11] Indeed the QK_4 is the mathematical sum of PEP and PTT where PTT is the time of transmission of the pulse wave from the aortic root to the antecubital fossa where the micro phone is placed. The changes in QK observed in the present study corresponds almost exactly to the *change in* PEP observed by Spodick and Quarry Pigott[8] and the change in PTT observed by Kroeker and Wood[11] when readings of QK_4 PEP and PTT are compared at comparable heart rate

The changes in PEP and PTT are both appar ently due to an increase in stroke output (for exercise while standing) and/or adrenergic stim ulation of the myocardium[12] The sensitivity of QK_4 to stroke output has been documented in studies of sympathomimetic agents such as epinephrine[3] isoproterenol[13] and ketamine[14] in studies of beta adrenergic blockade[15, 16] and in studies of thyroid disease[18, 19] The shortening of the QK_4 can not be accounted for solely on the



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basis of shortening of the isovolumic contraction intervals since, even if this interval were to shorten to near zero, the pulse wave velocity would still have to increase significantly to produce the observed results

The rise in systolic pressure recorded immediately after exercise can be attributed to the increased ejection rate which stretches and decreases the compliance of the aorta and the arterial tree and increases the arterial pulse wave velocity [20]

The first heart sound appears somewhat earlier in the cardiac cycle, advancing from 48 to 42 msec Total electromechanical systole also shortens, as indicated by the markedly earlier appearance of the second sound in the cardiac cycle The arterial pressure wave arrives at the brachial artery much earlier in the cardiac cycle, advancing from an average of 204 msec to approximately 160 msec Resting values of all parameters were regained within about 5 minutes after the exercise The data provide a basis for comparison with data obtained on patients with cardiovascular disease

A similar protocol was followed with more than 50 patients with cardiac disease In some of these studies, a standard two step test was used in lieu of treadmill exercise A great diversity of results were obtained as expected Usually changes in all parameters studied paralleled those in the normal group Some patients showed a significant delay in the return to baseline values

Advantages of the QK_d The QK_d is the sum of three definable intervals of the cardiac cycle the electromechanical lag (EML or QS_1), the isovolumic contraction time (IVCT or ICT) and pulse transmission time (PTT) Presumably changes could occur in these three intervals which tended to "cancel out Usually the changes are additive however so that misleading results are not obtained The QK_d has several advantages compared with the noninvasive measurement of PEP[7] as an index of cardiovascular response to exercise, drugs etc First it requires only two channels of information ECG and Korotkoff sounds, whereas the PEP requires ECG, phonocardiogram, and a recording of carotid pulsations Second, the QK_d involves determination of only two time points (1) onset of the QRS complex and (2) onset of Korotkoff sounds By contrast, measurement of PEP requires determination of the timing of at least four events (1) onset of QRS, (2) onset of high-frequency component of the second sound, (3) onset of carotid arterial pressure rise, and (4) moment of reaching the incisura of the dicrotic notch Each of these measurements entails errors of 5 to 10 ms , depending on paper speed, care in measurement, etc Further, the onsets of the QRS and of the Korotkoff sounds are usually much better defined than the onset of the second sound or the onset or dicrotic notch on the arterial pressure wave Also, with maximal exercise, the QK_d interval may change by as much as 100 ms. By contrast, the maximal change in PEP is rarely more than 50 ms This further reduces the effect of measurement errors Accordingly, the QK_d interval can be measured on a single beat" whereas measurements of systolic time interval requires measurement on 5 or 10 *selected* beats. In the sphygmorecording method[1,3] the blood pressure is measured automatically along with QK and QK_d The QK_d requires only about a minute to obtain a tracing (inflating and deflating the blood pressure cuff, and Polaroid photography of the oscilloscope)

Summary

An indirect, noninvasive method of sphygmorecording was used to study the effect of exercise on a number of cardiac parameters, including heart rate, blood pressure, the timing of the heart and Korotkoff arterial sounds, and the slope (dP/dt) of the brachial arterial pressure wave The QK_d interval is a sensitive and reliable indicator of the cardiovascular response to exercise stress, and can be used to follow the rate of return to basal levels Changes in the QK_d can occur even in the presence of fixed heart rate These studies provide a baseline for analysis of patients with cardiovascular disease

David Rodbard M D provided a critical review and assistance in the preparation of this manuscript Bruce Mount and James Barela were responsible for the development of the electronic apparatus used in these studies

REFERENCES

1 Rodbard S Rubinstein H M and Rosenblum S Arrival time and calibrated contour of the pulse wave determined indirectly from recordings of arterial compression sounds Am Heart J [illegible] 205 1957
2. Rodbard S and Mohrherr R Device for indirect registration of the calibrated arterial upstroke in man Rev Sci Instr 32 1022 1961
3 Rodbard S and Keller M F A new technique for the recording and analysis of heart sounds and murmurs Cardiologia 52 145 1968

Rodbard, S. Simultaneous recording of the heart and arterial sounds. (Submitted for publication)

Rodbard, S. and MacArthur, T. C. A device for objective indirect recording of the arterial pressure and related data, Med. Res. Eng. 8:20, 1969

Geddes, L. A., Knight, W., Posey, J., and Sutherland, N. Indirect determination of the rate of rise of arterial pressure, Cardiovasc. Res. Center Bull. 7:71, 1968.

7. Weissler, A. M., Harris, W. S., and Schoenfeld, C. D. Systolic time intervals in heart failure in man, Circulation 37:149, 1968.

8. Spodick, D. H., and Quarry Pigott, V. M. Effects of posture on exercise performance. Measurement by systolic time intervals, Circulation 48:74, 1973.

9. Maher, J. T., Beller, G. A., Ransil, B. J., and Hartley, L. H. Systolic time intervals during submaximal and maximal exercise in man, Am. Heart J. 87:334, 1974.

10. Bruce, R. A., Blackmon, J. R., Jones, J. W., and Strait, G. Exercising testing in adult normal subjects and cardiac patients, Pediatrics 32:742, 1963.

11. Kroeker, E. J., and Wood, E. H. Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man, Circ. Res. 3:623, 1955.

12. Harris, W. S., Schoenfeld, C. D., Brooks, R. H., and Weissler, A. M. Effect of beta adrenergic blockade on the hemodynamic responses to epinephrine in man, Am. J. Cardiol. 17:484, 1966.

13. Easley, R., and Rodbard, D. A critique of the hyperdynamic beta adrenergic circulatory state: New evidence by sphygmorecording. (Submitted for publication)

14. Henderson, J. B., Rodbard, S., and Morse, H. T. Effects of anesthesia and related procedures on arterial pressure wave arrival times, Anesth. Analg. 51:942, 19"2.

15. Keller, M. F., and Rodbard, S. Retardation of the arterial pressure wave by propranolol, Am. Heart J. 82:794, 1971.

16. Vana, S., Felt, V., Nemec, J., et al. Some effects of trimepranol and propranolol in thyrotoxicosis and patients with some arrhythmias, Cas. Lek. Cesk. 111:454, 19"2.

17. Rodbard, D., Fujita, T., and Rodbard, S. Estimation of thyroid function by timing the arterial sounds, J.A.M.A. 201:884, 1967.

18. Young, R. T., Van Herle, A., and Rodbard, D. Clinical diagnosis and management of hyperthyroidism by timing the arterial sounds, J. Clin. Endocrinol. Metab. (In press)

19. Vana, S., Nemec, J., Bednar, J., et al. Beziehung des Blutspiegels der Thyreoideahormone zur Verspätung des Korotkoff Tones, Endokrinologie [illegible]:111, 1971.

20. Cox, R. H. Wave propagation through a Newtonian fluid contained within a thick walled viscoelastic tube: The influence of wall compressibility, J. Biomech. 3:317, 1970.

Observations on the A2 England influenza epidemic

A CLINICOPATHOLOGICAL STUDY

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Mild influenza is a common disease from which recovery occurs in a few days and in which there are few recognized sequelae other than lassitude and depression, which may persist for a few weeks after the infection The involvement of the heart in cases of clinically severe Asian influenza epidemic was described by Giles and Shuttleworth[1] and clinical accounts of this and subsequent outbreaks of influenza have established that evidence of myocardial damage is not uncommon in patients admitted to hospital

The incidence of myocardial involvement in mild influenza has not been established One of the difficulties is the mixed nature of many epidemics which causes great difficulties in identifying the causal organism in individual cases We report here a study of a mild influenza epidemic due to A2 England influenza that occurred in Sheffield in the winter of 1972 1973 The histology of the myocardium in fatal cases is shown to be consistent with the electrocardiographic changes found in mild cases treated at home The findings indicate that myocarditis is a common event in mild influenza and may result in long lasting changes in the electrocardiogram (ECG)

Although the A2 England influenza virus caused a mild illness several fatal cases were encountered in Sheffield during the epidemic Five of these were studied and are presented in order of the duration of the illness before death Virus cultures were made in all cases but were positive in only one In our experience this low positive rate is usual in Coroner s cases where there is delay in performing the autopsy

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Case reports

Death within 24 hours of onset of illness

Case 1 S A P 9 years of age complained only of a sore throat, his symptoms were not considered serious The morning following the onset of the illness he was found dead in bed Autopsy showed gross tracheobronchitis with mucosal separation, typical of influenza There was massive hemorrhagic pulmonary edema Influenza A virus was grown from the lung

Microscopic examination of the heart showed no inflammatory reaction but individual myocardial fibrils showed fragmentation and loss of striation

Eosinophilic staining of the fibrils was not marked but early necrosis could be demonstrated by acid fuchsin staining[2, 3]

Case 2 D H 19 years of age had suffered from asthma in childhood but had had no recent illness He was found dead in bed having made no complaint the night before At autopsy there was gross acute tracheobronchitis with almost complete mucosal loss and massive hemorrhagic pulmonary edema The heart on naked eye examination showed only a few surface petechial hemorrhages but microscopy showed marked

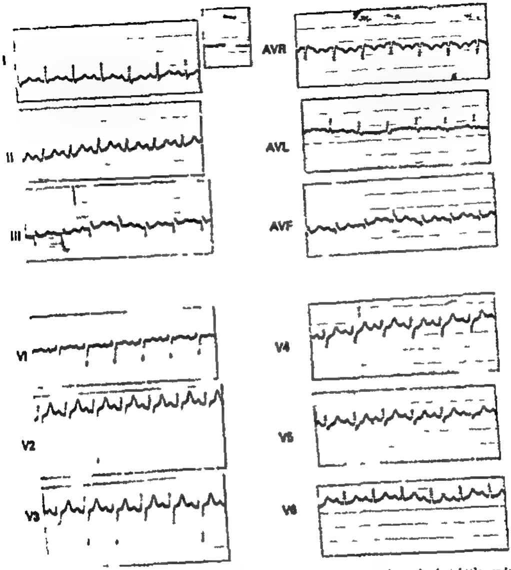


Fig 1 ECG recorded 3 hours before death (fatal case No 3) There is a tachycardia but little evidence of myocardial damage.

interstitial hemorrhages and edema with loss of striation and fuchsinophilia There was no fragmentation of the myofibrils

Deaths on fifth day of illness

Case 3 D M a 52 year old housewife contracted acute influenza and was treated at home with antibiotics for 5 days Her clinical condition deteriorated and on the fifth day of the illness she collapsed She was admitted to hospital semiconscious with central cyanosis and evidence of extreme right and left cardiac failure Attempts to resuscitate her were unsuccessful and she died on the day of admission The ECG which was recorded shortly before death showed a tachycardia but was otherwise within normal limits (Fig 1)

At autopsy the trachea and main bronchus showed velvety inflammation the lungs were congested but showed no inflammatory reaction The heart was soft on palpation and on microscopy showed gross changes with fragmentation of the myofibrils and marked fuchsinophilia Interstitial hemorrhage and edema were present (Fig 2)

Case 4 A R a 45-year old man with chronic bronchitis died on the fifth day of an influenzal

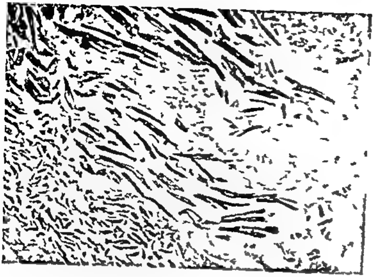


Fig 2 Myocardium from fatal case No 3 Generalized changes were present throughout the heart

Table I Symptoms in 42 cases of influenza treated at home

	Mild (3 cases)	*Moderate (21 cases)*	*Severe (18 cases)*	*Total*
Pyrexia	3	21	18	42
Cough	3	21	18	42
Myalgia	3	21	16	40
Headache	3	21	16	40
Diarrhea	1	2	0	3
Vomiting	0	4	5	9
Tachycardia	1	7	6	14
Bradycardia	0	3	4	7

illness At autopsy there was very gross tracheitis with mucosal loss The lungs showed extensive hemorrhagic edema Microscopic examination of the heart showed fragmentation of the myofibrils marked fuchsinophilia and extensive interstitial hemorrhage There was no inflammatory reaction

Death on eighteenth day of illness

Case 5 D H, a 22 year old man was admitted to hospital with a staphylococcal pneumonia 4 days after showing influenza symptoms Despite intensive chemotherapy, he died 18 days after the onset At autopsy the myocardium was found to be mainly normal but there were occasional perivascular accumulations of inflammatory cells

Clinical study

The study was begun during December, 1972 in a general practice close to the hospital Fifty consecutive patients were studied They comprised the first 50 in the epidemic diagnosed as influenza and were seen between late December, 1972, and early February, 1973 At the first visit, in response to the patient's call an ECG was recorded A 10 ml sample of blood was taken for serology Arrangements were made for a ECG and a further blood sample to be obtained approximately 10 to 21 days later Following this, patients were asked to attend the hospital approximately 3 to 6 weeks later for a chest x ray and third ECG All ECG's were recorded with the patient recumbent

The following symptoms were recorded pyrexia, myalgia, headache, diarrhea, vomiting and cough (Table I) The illness was assessed as mild, moderate, or severe on the basis of clinical examination, although these were degrees of mildness, no patient requiring hospital admission or to remain in bed for more than 2 days

Serological tests on the blood samples

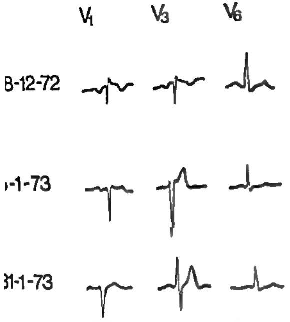
Influenzal infection was established by positive hemagglutination inhibition (HI) tests and complement fixation (CF) tests with standard techniques[4]

A fourfold or greater rise in HI titer in serial samples was found in 39 patients who were thus considered to have influenza The sera of HI negative patients were tested for CF antibody A fourfold or greater rise was found in serial samples of three patients who were included in the positive group which thus comprised 42 patients

Results

All the patients seen were treated at home for an illness which was not sufficiently severe to merit admission to hospital The eight who proved to have negative serology had a mild influenza like illness similar to those who were positive Our analysis is confined to the 42 positive cases One patient, who was admitted to hospital because she developed complete heart block is referred to in discussion where it is relevant She also showed positive HI titers to A2/England/42/72 influenza Her general practitioner reported that some years earlier a normal heart rate of 70 had been recorded

Eighteen patients were female (42 9 per cent) and 24 were male (57 1 per cent) The average age of the whole group was 44 4 years (range 15 to 72 years) the majority 24 patients were between 30 and 59 years



g 3. Domiciliary series No 3. Progressive recovery in P ave and ST changes over 1 month from initial record during cute illness.

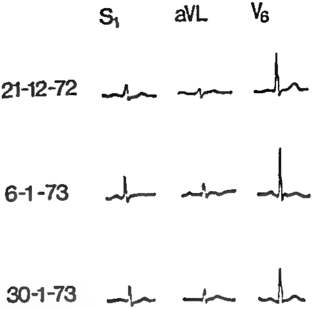


Fig 4 Domiciliary series No 8 Flattening of T waves with inversion in aV_L seen on second visit (June 1 19 3) and subsequent recovery

The *clinical features* (Table I) of the illness were a sustained fever rising usually to 40 or 41° in a few hours with myalgia headache and cough as usual symptoms. One third of the patients had a tachycardia of over 100 per minute and one in six a bradycardia of less than 60 beats per minute in the acute stage of the illness Diarrhea or vomiting were seen occasionally After 2 to 3 days there was a rapid recovery with return of the temperature to normal limits. All patients were ambulant by the fourth day of illness and had returned to their normal occupations at the end of 1 week

The initial ECG was recorded within 48 hours of onset of symptoms in 25 (59 5 per cent) and within 72 hours in 34 (81 per cent) In only two was it as long as 5 days The second recording was made between 10 and 21 days of onset of symptoms in 35 (83 3) In only two was this time greater than 28 days The time between the first and second tracings was 10 to 21 days in 37 (88 1 per cent) between the second and third tracings 3 to 4 weeks in 18 out of 34 patients (52 9 per cent) and 4 to 5 weeks in 12 (35 5 per cent) In only four (11.8 per cent) was it longer than this—three at 5 to 6 weeks and one at 6 to 7 weeks

The ECG findings were divided into three groups (1) normal throughout the illness (2) long standing abnormalities, (3) transient changes.

Normal ECG s were recorded in 24 people 15 women and 9 men Their average age was 47 years, the average for all patients being 44 years (range, 15 to 67 for men and 17 to 72 for women) The influenzal illness was graded in this group as severe in 8 moderate in 14 and mild in 2

Long standing ECG changes were found in five patients These were related to chronic bronchitis in three cases one patient was in established atrial fibrillation one had hypertension with myocardial ischemia and one had healed pulmonary tuberculosis with generalized ischemic vascular disease These pre existing illnesses were documented in the patients N H.S notes. As might be expected influenza tended to be a serious disease in these patients Four were considered severely ill and one moderately ill. In addition three of these patients showed transient ECG changes in the course of their influenza These transient changes were considered to be due to the acute infection and the three patients are therefore included in the next group

Transient ECG changes were seen in 18 of the 42 patients treated at home (43 per cent) The findings, including those from a patient with complete heart block who was admitted to hospi

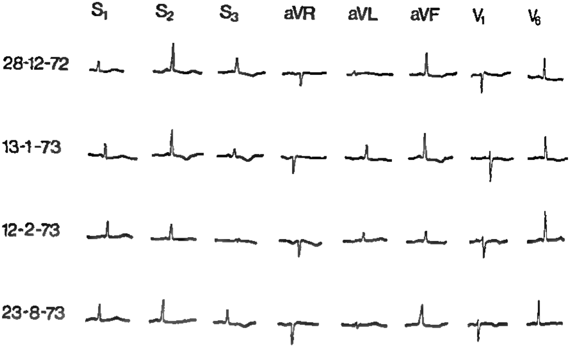


Fig ▪ Domiciliary series No 11 Generalized changes with T wave inversion in S_3 and aV_F and a variable pattern in V_1 and V_6 Nine months after the attack the ECG suggests posteroseptal damage

tal, are shown in Table II The changes included ST segment deviation, T wave inversion, flattening of the T wave sinus bradycardia, nodal rhythm, atrial fibrillation, and complete atrioventricular dissociation (Table II and Figs 3 to 5) One patient (No 2) was in atrial fibrillation throughout the period of study This arrhythmia had been present for some years The other patients with pre existing ECG abnormalities were No 6 with left ventricular hypertrophy, and No 18, who had evidence of an old anterolateral infarction In the group of 18 patients with transient ECG changes 10 (56 per cent) were judged to have severe influenza and eight (44 per cent) were moderately ill This is a slightly higher incidence of severe illness than was found in the group as a whole, where 50 per cent were moderately ill and 42 per cent severely ill (Table I) The ages ranged from 15 to 71 (mean, 44) 13 were men and 5 were women

A striking feature in the ECG changes found in this group is the frequency of evidence of local damage Only one patient (Fig 5) showed generalized ECG changes There was a high incidence of changes in the seven patients with bradycardia (five out of seven—71 per cent—Table II) In two patients (Nos 6 and 11) the ECG was still abnormal 8 weeks after the onset of the illness when the third ECG was recorded In No 11, ECG changes were still obvious 8 months after the initial attack (Fig 5) In No 6 no change attributable to the influenza was present after 9 months

A chest radiograph was taken at the time of the third ECG in 34 patients None showed changes that could be confidently related to the influenza

Discussion

When death occurs in influenza so suddenly that the diagnosis is made only at autopsy, the cause is most likely to be massive hemorrhagic pulmonary edema, but even in these cases changes are already present in the myocardium (Fatal cases 1 and 2) Deaths later in the illness may be the result of myocardial failure, as in case 3 The earlier changes, seen in the first 24 hours, are petechial hemorrhages and fuchsinophilia, with loss of striation of the myofibrils Fragmentation may be present At 5 days fragmentation is marked and there is interstitial edema and hemorrhage By the eighteenth day of the illness (case 5) the heart may appear more or less normal but occasional perivascular collections of inflammatory cells may be found This agrees well with the findings of Oseasohn and associates,[5] who found evidence of myocarditis in 10 of their 33 cases who died in the first 8 days of the illness Martin and associates[6] also found myocardial changes in Asian influenza identical with those reported here Giles and Shuttleworth[7] likewise reported myocarditis in one patient who died on

le II ECG changes in cases showing transient variation

Case	Age (yr)	Sex	Severity	First ECG Rhythm	First ECG Pattern†	Second ECG Rhythm	Second ECG Pattern	Third ECG Rhythm	Third ECG Pattern
1		M	+++	SB	N	S	C F II III aV F V	[illegible]	N
[illegible]	[illegible]	M	+++	AF	F II V V B V V	AF	R	AF	N
3	44	M	+++	S	A II III aV V V D V V E V	S	D V V	S	N
4	17	M	++	S	F II V D III	S	N	–	–
5	25	M	+++	S	D V V E V V3	[illegible]	D V F I V	S	N
6	65	M	+++	S	F II III aV E V	S	R	S	C I aV V V
7	32	F	++	S	F II III aV V	S	N	S	N
8	50	F	++	SB	E aV V	S	E AV F S	S	N
9	[illegible]	M	++	SB	F aV V	S	E aV F I V V	S	N
10	[illegible]	F	+++	[illegible]	F II III aV V	S	N	S	N
11	38	F	+++	SB	F all leads B all leads	S	B all leads E II III aV V V	S	E V F all leads
12	60	M	++	S	E aV F S	S	D V V	–	–
13	[illegible]	F	++	S	E V	S	F V	[illegible]	N
14	[illegible]	M	+++	SB	E V	S	N	S	N
15	[illegible]	M	+++	AF	F V V	S	N	S	N
16	56	M	++	SG	F V	S	N	S	N
17	40	M	++	SB	N	S	N	S	N
18	68	M	+++	SB	Old AL infarct	S	ISQ	S	ISQ
19‡	66	F	++	CHB	LBBB	ISQ		ISQ	

S, Sinus rhythm SB, sinus bradycardia AF atrial fibrillation CHB complete heart block G ventricular extrasystoles.
A, Abnormal P wave voltage B low voltage QRS C S-T segment depression D S-T segment elevation E, T wave inversion F low voltage T wave.
Admitted to hospital for permanent endocardial pacemaker

he eleventh day of the illness. The myocarditis may be generalized or as in some of the cases described by Oseasohn and associates may have a patchy distribution

A similar progression is seen in our clinical study Sinus tachycardia with a normal ECG throughout the illness occurred in only two cases in a domiciliary study as well as the fatal case in which patient a generalized myocarditis was found (fatal case No 3) Changing ECG patterns suggesting local damage were found early in the disease in 18 cases The changes were largely disturbances of normal rhythm and deviations of the ST segment and transient T wave inversion resembling those described in cases of Asian influenza.[5-9] Coltman Heinecker and Kemper [9] and Lewis Rainford, and Lane[11] have also reported abnormal ECG s in hospitalized cases of influenza The incidence of ECG changes reported in these studies varies from 14[9] to 75 per cent.[7] Our results are not strictly comparable with those described above however Each of these studies relates to hospitalized—and therefore presumably ill—patients, whereas the objective of our clinical study was to examine a group of patients whose illness was sufficiently mild that admission to hospital was not required Different studies relate to different strains of the influenza virus The incidence of ECG changes observed by us (43 per cent) in patients with mild influenza suggests that clinical severity per se is not a major factor in determining their occurrence

Lasting changes occurred in two of our patients. In one these resembled the effects of myocardial ischemia and would give rise to great

diagnostic difficulty if the significance of the mild influenzal illness was overlooked In the other, complete heart block requiring permanent pace making has occurred The reports on the myocar dium in heart block of Davies and Harris[12] and of Harris, Davis, Redwood, and Leatham[13] described patchy fibrosis which involved the conducting mechanism It is likely that the resolution of the acute myocarditis of influenza could cause such patchy fibrosis in occasional cases Thus a tran sient myocarditis appears to be common in in fluenza in the first 2 weeks of the infection In other cases there may be ECG evidence of more prolonged damage to the myocardium In our patients, long lasting ECG changes were not asso ciated with clinical heart disease Chronic cardio myopathy has, however been described in in fluenza [illegible] The evidence that cardiac failure may develop or persist after acute viral myocarditis is best documented in Coxsackie virus group B infections[17, illegible] A similar sequence of events has been described in arbovirus infection[19] In many clinically similar cases however, there is no evidence of recent viral illness Several factors may militate against establishing a viral etiology in these cases virus infections are often subclini cal, isolation of some viruses is difficult and patients are often first seen too long after a suspected virus illness to prove a viral etiology by currently available serological methods The present study has shown that a minor illness which may readily be forgotten does not preclude the development of ECG changes suggestive of myocardial damage

Lewes and associates[11] and Lewis and Rain ford[15] have drawn attention to the role of a number of virus infections in producing changes suggestive of ischemic heart disease The present work shows that these changes may result from trivial influenzal illnesses lasting only a day or two The diagnostic problem set by such effects is a formidable one

Summary

A clinicopathological study of the 1972 1973 A2 England influenza epidemic is presented In fatal cases early necrosis of myofibrils was present in those patients who died within 24 hours of the onset of the influenza symptoms At 5 days gross changes were present These were largely resolved by the eighteenth day of illness

In 42 patients treated at home transient ECG changes were found in 18 cases These included ST segment deviation, T wave inversion fla tening of the T wave, sinus bradycardia o tachycardia, nodal rhythm, and atrial fibrillat Permanent changes were observed in one pat and in an additional patient admitted to hospi with permanent A V block

REFERENCES

1 Giles C and Shuttleworth E M Post mort in 46 influenzal deaths Lancet 2 1?24 1957
2 Neilson K Renaud G Lemire Y, and Seyle P Fuchsinophilic degeneration of myocardial fibres, P Can Fed Biol Sci Kingston Ont June 9 11 1958
3 Poley H W Fobes D and Hall M J Fuchsinoph in early myocardial infarction Arch. Pathol. 77 1964
4 Sever J L Application of a microtechnique to r serological investigations J Immunol [illegible] 3?0 1962
5 Oseasohn R H Adelson L and Kaji M Clinicopath logical study of 33 fetal cases of Asian influenza, N E J Med 260 509 1959
6. Martin C M Kunin C M Gottlieb L S Barne M W Liu C and Finland M Asian influenza A Boston 1957 58 Observations in thirty two influenza associated fatal cases Arch Intern Med. 103 1959
7 Walsh J Burch G F White A Mogabgab W a Digtlein L A study of the effects of type A (strain) influenza on the cardiovascular system of Ann Intern Med 49 502 1958
8 Gibson T C Arnold J Craige E and Curnen G C Electrocardiographic studies in Asian influenza, Am Heart J 57 661 1959
9 Coltman C A Influenza myocarditis Report of a case with observations on the serum glutamic oxalo ace transaminase J A M A 180 204 196?
10 Heinecker R and Kemper F Uber den Einfluss de influenza Dtsch Med Wochenschr 81 ?03 1956
11 Lewis D Rainford D J and Lane W F Symptomless myocarditis and myalgia in viral and mycoplasma pne monia infections Br Heart J 36 9?1 1974
12 Davies M and Harris A Pathological basis of primary heart block Br Heart J 31 219 1969
13 Harris A Davies M Redwood D Leatham A and Siddons, H Aetiology of chronic heart block A clinico pathological correlation of 65 cases Br Heart J 31 1969
14 Burch G E Giles T D and Colcolough H L Pathogenesis of rheumatic heart disease critique and theory Am Heart J 80 556 1970
15 Lewis D and Rainford D J Echoviruses and carditis Lancet 1 520 1970
16 Finland M Parker E Barnes M W and Joliffe L S Acute myocarditis in influenza A infections Am J Med Sci 209 455 1945
17 Sainani G S Krompstie E and Slodki S J Adult heart disease due to Coxsackie virus B infection Medi cine 47 133 1968
18 Lerner A M Wilson F M and Lyes M P Enterovi ruses and the heart (with special emphasis on the probable role of Coxsackie viruses group B types 1 5) Mod Concepts Cardiovasc Dis 44 11 1975
19 Obeyesekere I and Hermon Y Arbovirus heart disease Myocarditis and cardiomyopathy following den gue and Chikungunga fever—a follow up study Heart J 85 186 1973

...vave terminal force and persisting ST ...vations in chronic ischemic heart disease

...EDICTION OF LEFT VENTRICULAR MOTILITY AND ...ASTOLIC PRESSURE

...lbjorn Forfang M D
...nnar Stake M D
... Norway

...nce Morris and associates[1] in 1964 introduced ...e term P terminal force (Ptf) an abnormal ...tf in V (V Ptf) is demonstrated in several left ...ded heart lesions both acute and chronic In ...chemic heart disease Bethell and Nixon found ...hat the P wave may be the first component of ...he electrocardiogram (ECG) to become abnor...mal and they stated that an abnormal V Ptf in ... apparently healthy subject should lead to ...uspicion of ischemic heart disease and further ...nvestigations In acute myocardial infarction V,Ptf correlates well with pulmonary wedge pres...sure[4-7] and in pure aortic stenosis a good correla...tion is demonstrated between V Ptf and left ...entricular end diastolic pressure (LVEDP)[8] ST ...levations have been widely used as sign of left ...entricular aneurysm

The purposes of this study were (1) to investi...gate the ability of V Ptf to predict particular ...hemodynamic changes in chronic ischemic heart ...disease and (2) to further assess the clinical value ...of V Ptf in the evaluation of patients in compar...ison with persisting ST elevations

Material and methods

In a prospective study 80 male patients hospitalized for coronary heart disease have been studied Their ages ranged from 28 to 69 years (mean 50) All of them had a typical history of

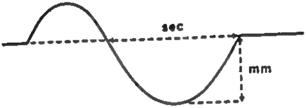


Fig 1 Measurements for calculation of V Ptf

angina pectoris and 59 had previously had at least one myocardial infarction No infarction had occurred during the last 3 months before admission to the hospital and all were in sinus rhythm

ECG s were recorded with a direct writing ink jet Mingograf (Elema Schonander) with a paper speed of 50 mm per second within 1 to 3 days before the hemodynamic study No change in the clinical picture occurred during this period in any of the individuals

The estimations of P wave terminal force in V_1 (V Ptf) were made according to the method of Morris and associates using a hand magnifying lens Measurements of amplitude and duration were made to the nearest 0 5 mm up and down The terminal force is defined as the product of the amplitude in millimeters (1 mm = 0 1 mV) and the duration in seconds of the terminal portion of the P wave (Fig 1) Normal V Ptf value is defined as $>$ −0 03 mm second The mean of five successive P waves was used in each case The measurements were done blindly without knowing the results of the hemodynamic investigation Like Morris and associates[1] we found good repro

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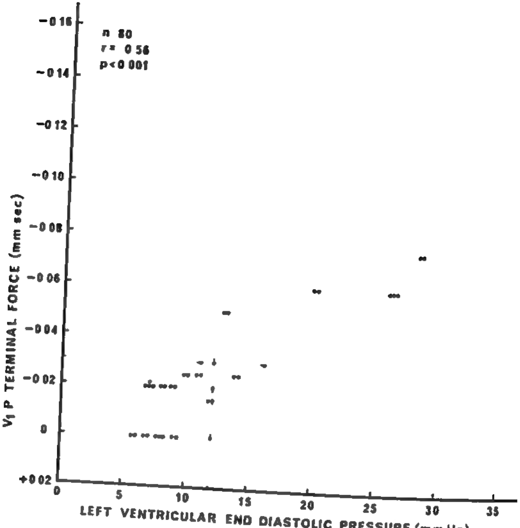

Fig 2 Correlation between V Ptf and LVEDP

ducibility of the measurements P waves from 38 patients were measured blindly twice and by linear correlation analysis the correlation coefficient was 0 96(x = 0 96y + 0 0021)

Pathological ST elevations were noted if they occurred in Leads II and III and/or in one or more of the precordial leads from V_3 to V_6 provided they fulfilled one of the criteria Horizontal elevation 2 mm or more or ascending ST segments with starting points 2 mm or more above the baseline Such ST elevations may be indicative of left ventricular aneurysm

Retrograde catheterization of the left ventricle and selective coronary arteriography were made as follows The left ventricle was catheterized via the left femoral artery with a Pigtail Ducor 8 F catheter

After pressure recordings a ventriculogram was made with the patient in the right anterior oblique (RAO) position, with 35 mm film and 75 frames per second A 45 ml quantity of Isopaque Coronar (metrizoate meglumine/Na/Ca (58/9/1) 370 mg J/ml) was injected by a pressure injector (Gidlund) (8 Kg per square centimeter) In cases where ventriculography in the RAO position led to suspicion of ventricular aneurysm an additional injection was made in the left anterior oblique (LAO) position Selective coronary arteriography was made according to the method described by Judkins [11]

The pressure recordings were made with an Elema Schonander pressure transducer EMT 35 No 2359 with zero reference level on the anterior axillary line in the fourth intercostal space Left ventricular end diastolic pressure (LVEDP) was measured after the a wave just prior to the rapid systolic upstroke taking the mean pressure of five successive cycles

Ejection fraction (EF) was measured by planimetry with the use of the ellipsoidal formula for calculation according to the method of Arbogast and associates [1]

With reference to the findings during ventriculography the patients were divided into two

ips. Group 1 (dyskinesia group) contains all ents with EF less than 50 per cent and/or i aneurysm of the left ventricular wall with ing contour and paradoxical movements The of the patients all with EF above 50 per cent ong to Group 2

he statistical evaluations were made by linear relation analysis and t test

ults

eft ventricular aneurysm was found in 14 pa nts and in addition 12 had EF below 50 per it bringing the content of Group 1 to 26 tients In this group EF ranged from 5 to 56 per it (mean 27 per cent) In only two patients EF is above 40 per cent and they both had aneu m (EF 47 and 56 per cent respectively) Group patients with EF above 50 per cent and without eurysm) consisted of 54 patients Abnormal Ptf (< −0 03 mm second) was found in 27 itients and elevated LVEDP (above 12 mm g) in 37 (Fig 2) A more detailed study of rrelations between angiographic findings and astolic left ventricular pressures will be iblished elsewhere

Fig 2 shows the correlation between V Ptf and VEDP This correlation is statistically signifi ant with correlation coefficient r = −0 56 a = 80 p < 0 001 95 per cent confidence inter al −0 39 to −0 69) If V Ptf more negative than 0 03 mm per second was used to detect elevated VEDP the sensitivity was 59 per cent (22 of 37) and the specificity was 88 per cent (five of 43 false positive)

In the dyskinesia group mean V Ptf was −0 058 mm per second in contrast to −0 021 mm second in the group with EF above 50 per cent (Fig 3) This difference is highly significant ($p < 0.001$) When using V Ptf<−0 03 mm second to separate patients belonging to the dyskinesia group from patients in Group 2 the sensitivity was 73 per cent (19 of 26) and the specificity 83 per cent (nine of 54 false positive)

Fig 4 shows the relationship between V Ptf and LVEDP in the dyskinesia group Twenty three patients had elevated LVEDP and in 18 of them V Ptf was more negative than −0 03 (73 per cent) As shown in the same figure pathological ST elevations suggesting left ventricular aneurysm occurred in nine of 14 patients (64 per cent) with angiographically demonstrable aneurysm Similar ST elevations were also found in five of 12

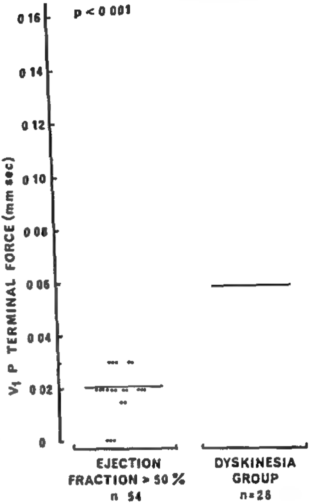

Fig 3 V Ptf in the dyskinesia group compared with the group with EF above 50 per cent

patients (42 per cent) with EF below 50 per cent without detectable aneurysm Consequently in using ST elevations to detect aneurysms or EF below 50 per cent we found a sensitivity of 54 per cent (14 of 26) The specificity was excellent because only one of the 54 patients in Group 2 displayed these ST elevations.

Discussion

Abnormal V Ptf is found in various left sided heart lesions both acute and chronic[1,9] In our material however V_1Ptf was of poor value as a parameter to separate individuals with ischemic heart disease from others because only 27 of our 80 patients displayed abnormal V_1Ptf

Nevertheless V Ptf used as a sign of elevated LVEDP with sensitivity 59 per cent and specif icity 88 per cent is as good an electrocardiographic

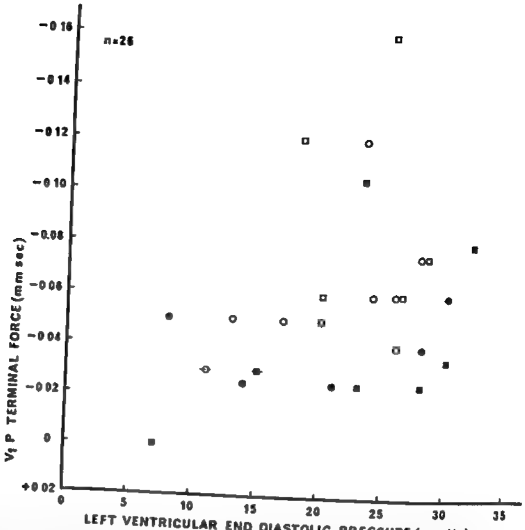

Fig 4 Relationship between V Ptf and LVEDP in the dyskinesia group differentiating between akinesia and aneurysm with and without abnormal ST elevations Symbols Clear circles aneurysm with ST elevations black circles aneurysm without ST elevations clear squares akinesia (EF < 50 per cent) with ST elevations black squares akinesia (EF < 50 per cent) without ST elevations

parameter as many commonly used parameters of left ventricular hypertrophy [14] The significance of the correlation between V_1Ptf and LVEDP in our material is at the same level as earlier found in pure aortic stenosis [8]

The main mechanism for abnormal V_1Ptf in left ventricular disease is said to be dilatation of the left atrium [9] In coronary heart disease and especially in cases with hypokinetic ventricle or aneurysm the left ventricular compliance is reduced [15 16] and an increased end diastolic pressure is required to achieve a sufficient end diastolic volume The elevated filling pressure is achieved by increased force of left atrial contraction, and may by Frank Starling mechanism lead to increased left atrial volume Left atrial volume increments usually occur in a posterior direction thus leading to a posterior rotation of the P vector in the horizontal plane

The differentiation between aneurysm and akinesia by ventriculography is difficult and unreliable, and in fact aneurysms may appear as only akinetic areas [19] The clinical importance is related to the extent of the noncontracting part of the left ventricular wall

The considerable reduction of compliance in aneurysms and hypokinetic ventricles probably explains why V_1Ptf is a good parameter to separate the dyskinesia group from the other, with a sensitivity of 73 per cent and specificity 83 per cent (nine of 54 false positive) The specificity increases inversely proportionally to the V_1Ptf value Our seven patients with V_1Ptf < −0 0[illegible] mm second all belong to the dyskinesia group (Fig 3) Abnormal ST elevations are in this respect more specific (98 per cent) but considerably less sensitive (54 per cent) than V_1Ptf <−0 03 mm second Similar sensitivity of ST elevations at rest was found by Gorlin and associates[19] in diagnosing left ventricular aneurysms

jection fraction (EF) is found to be useful as a nostic guide in aortocoronary bypass sur ,[20] Bedside signs of reduced EF will therefore valuable Abnormal ST elevations and/or ormal V Ptf can be used in this way with a ier high specificity

nmary

n [illegible] male patients with coronary heart disease erminal force in V_1 (V_1Ptf) was correlated with ventricular end diastolic pressure (LVEDP) d the findings by left ventricular angiography ection fraction [EF] and signs of aneurysm) e correlation between V Ptf and LVEDP was tistically significant (r = – 0 56 n = 80 < 0 001) Abnormal V Ptf (< –0 03 mm cond) used to detect LVEDP > 12 mm Hg ve sensitivity 59 per cent (22 of 37) and specif ty 88 per cent (5 of 43 false positive) The mean Ptf in 26 patients with aneurysm and/or EF < per cent (dyskinesia group) was –0 058 mm cond in contrast to –0 021 in patients with EF [illegible] per cent (p < 0 001) Abnormal V Ptf was a ore sensitive parameter in separating the dyski esia group from the others than abnormal ST evations (sensitivity 73 vs. 54 per cent respec vely) but less specific (83 vs. 98 per cent) In this aspect the specificity of V_1Ptf increases inversely roportionally to the V Ptf value Both of these lectrocardiographic parameters may be useful in he primary selection of patients suited for urgical treatment of coronary heart disease

EFERENCES

1 Morris, J J Jr Estes, E H Jr Thompson H K Jr and McIntosh, H D P wave analysis in valvular heart disease Circulation [illegible] 242, 1964

2 Gooch A. S Calatayud, J B Rogers J B and Gorman, P A. Analysis of the P wave in severe aortic stenosis, Dis. Chest 49 459 1966

3 Tarazi, R. C Miller A Frolich, E D and Dustan H. P Electrocardiographic changes reflecting left atrial abnormality in hypertension Circulation 34 818 1966

4 Heikkila J Mitral incompetence as a complication of acute myocardial infarction Acta Med Scand Suppl 475 65 1967

5 Bethell H J N and Nixon P G F P wave of electrocardiogram in early ischaemic heart disease Br Heart J 34 1170 1972

6 Chandraratna, P A N., and Hodges, M Electrocardiographic evidence of left atrial hypertension in acute myocardial infarction, Circulation 47 493 1973

7 Heikkilä J., Hugenholtz, P G and Tabakin B S Prediction of left heart filling pressure and its sequential changes in acute myocardial infarction from the terminal force of the P wave Br Heart J 35 142, 19 3

8 Yokoyama M., Sakamoto A., Konno S., and Sakakibara S P wave changes on exercise in patients with isolated mitral stenosis, Am Heart J 87 15 1974

9 Forfang, K., and Simonsen S Correlation between P wave terminal force and hemodynamic parameters in aortic stenosis, Prediction of left ventricular end-diastolic pressure, Cardiology [illegible] 222, [illegible] 4

10 Friedeberg, C K. Diseases of the heart Philadelphia and London, 1966, W B Saunders Company p 808.

11 Judkins, M P Selective coronary arteriography A percutaneous transfemoral technic, Radiology 89 815 1967

12 Arbogast, R., Solignac, A., and Bourassa M G Influence of aortocoronary saphenous vein bypass surgery on left ventricular volumes and ejection fraction. Comparison before and one year after surgery in 51 patients, Am J Med. 54 290 1973

13 Forfang, K., Andersen A Simonsen S and Stake G Relationship between left ventricular filling pressure and angiographic findings in coronary heart disease Ventriculography used as a stress test. To be published.

14 Romhilt, D W., Bove K E., Norris, R J., Conyers, E., Conradi, S Rowlands, D T., and Scott R C A critical appraisal of the electrocardiographic criteria for the diagnosis of left ventricular hypertrophy Circulation 40 185 1969

15 Klein M. D., Herman, M V., and Gorlin, R A hemodynamic study of ventricular aneurysm Circulation 35 614 1967

16 Bristow J D Van Zee B E., and Judkins, M P Systolic and diastolic abnormalities of the left ventricle in coronary artery disease. Studies in patients with little or no enlargement of ventricular volume, Circulation 42 219 19 0

17 Diamond, G., and Forrester J S Effect of coronary artery disease and acute myocardial infarction on left ventricular compliance in man, Circulation 45 11 1972

18 Smith, M., Russel R. O., Jr., Moraski, R. E Feild B J., and Rackley C E. Left ventricular P wave amplitude in patients after myocardial infarction, Am J Cardiol, 33 3 0 1974

19 Gorlin R Klein M D and Sullivan J M Prospective correlative study of ventricular aneurysm Mechanistic concept and clinical recognition Am. J Med 42 512, 1967

20 Cohn P F., Gorlin R., Cohn L. H., and Collins, J J., Jr Left ventricular ejection fraction as a prognostic guide in surgical treatment of coronary heart disease Am J Cardiol. 34 136 1974

The natural history of small atrial septal defects Long-term follow-up with serial heart catheterizations

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The question of operation upon the small atrial septal defect (ASD) has recently been raised by Moss and Siassi[1] 'The small atrial septal defect—operate or procrastinate?" One advocate of operation argues that an ASD with a left to right shunt of more than 30 per cent of the pulmonary flow should "unconditionally' be operated upon because of the risk of developing pulmonary hypertension or infection[2] Similarly, Gasul and associates[3] stated that, ' Because of the satisfactory surgical results, closure of the defect is mandatory Therefore the indication for surgery is the *diagnosis* of an uncomplicated atrial septal defect, irrespective of whether it belongs to the fossa ovalis the sinus venosus, or the ostium primum variety ' Nadas and Fyler,[4] on the other hand, recommend operation only when the pulmonary to systemic flow ratio (PSFR) is at least 2 0 1

In order to contribute to the clarification of this question we wish to report a long term follow up of 39 patients with small ASD s, including serial heart catheterization in 26 cases

Material

The material includes all the 39 patients in whom the diagnosis of an isolated small ASD of the secundum type was established by heart catheterization in our laboratory between 19[illegible] and 1964 (both years included) as it has been o[illegible] policy not to operate upon patients with small ASD's The follow up period ended in 1969 giv[illegible] a minimal follow up period of 5 years

The following criteria for inclusion were applied

1 A left to right shunt on the atrial level as demonstrated by the average percentage of oxygen saturation being at least 5 per cent higher in the pulmonary artery than in the caval veins

2 A PSFR of less than 2 0

3 A peak systolic pressure gradient between right ventricle and the pulmonary artery of less than 30 mm Hg (or less than 15 mm Hg w[illegible] PSFR below 1 5)

4 No auscultatory or phonocardiographic evidence of ventricular septal defect

5 A QRS frontal axis of more than –15°

6 Normal pressure in the pulmonary artery

7 Absence of any other cardiovascular anomaly

The above criteria do not exclude the possible presence of a left to right shunt to the caval veins

The age of the patients at the initial study varied between 4 and 46 years (Fig 1) 26 were female and 13 male At the initial clinical examination no patient had signs of right heart failure four patients complained of slight exertional dyspnea (PSFR being 1 8, 1 6, 1 8 and 1 6, respectively) Electrocardiographically eight patients had RVH and six RBBB (Table I) Roentgenograms of the chest were available for review

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ll except two patients. Cardiomegaly was d in seven a prominent pulmonary artery ient was registered in 10 and the pulmonary ular markings were increased in two patients ble I)

hods

he patients were traced through the public stration offices. Those alive were invited to a ical examination consisting of evaluation of liac symptoms physical examination electro liogram (ECG) and roentgenogram of the st a new heart catheterization was then tinely advised Those patients who refused to irn for the clinical examination were asked to wer a questionnaire

ight heart catheterization was performed as viously described.[5] It is to be emphasized that routine in our laboratory for shunt calcula n is to use samples from both the superior vena a and the inferior vena cava to calculate the xed systemic venous blood The reliability of FR determination was examined in 30 pa nts in each of whom two series of blood mples were obtained during one heart catheter ation Had only one series been available for lculation of PSFR the standard deviation D) would have been 0 34 When two series used for PSFR calculation the S D was 24

esults

All of the 39 patients were traced the mean llow up period was 11 years (range 5 to 21) ig 1) Two patients had died one died 8 years ollowing the initial study in diabetic coma ithout evidence of cardiac deterioration the ther patient died following cardiac surgery (case —this patient will be discussed later) Among the emaining 37 patients 27 had a clinical examina ion and the remaining 10 answered the question aire Serial heart catheterization was performed h 26 patients with a mean follow up period of 9 8 ears (Fig 1) in six of these patients three atheterizations were carried out during the ollow up period but only the first and last studies were analyzed

Clinical findings No patient developed signs of right heart failure Three patients complained of slight exertional dyspnea at the follow up study two of these patients also had this complaint at the initial examination and in the third the ECG and roentgenological findings were unchanged (his PSFR was initially 1 6 recatheterization was not performed) The ECG findings were un changed in all patients Satisfactory roentgeno grams of the chest at the initial study as well as at the follow up examination were available in only 20 cases (Table II) no evidence of deterioration was present

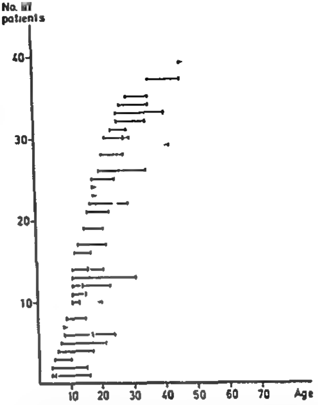

Fig 1 Distribution of the 39 patients according to the age at the initial heart catheterization and at follow up Solid line indicates that follow up includes recatheterization. A vertical line during the follow up period indicates an extra catheteri zation (six patients) Two patients (Nos. 10 and 11 from below) were followed clinically for 7 and 11 years—after their second catheterization only the latter one is included in the presentation of the 26 patients with serial heart catheteriza tions, because the second catheterization in the former one was carried out less than 5 years after the first catheteriza tion.

Hemodynamic findings These are shown in Table III and Fig 2 In three patients no definite intracardiac shunt was detected by oxygen exam ination (PSFR < 1 3) At the follow up study six patients had a PSFR of 2 0 or more in the re maining 17 patients the PSFR remained below 2 0 The pressures in the pulmonary artery and the right atrium remained almost unchanged as seen in Table III

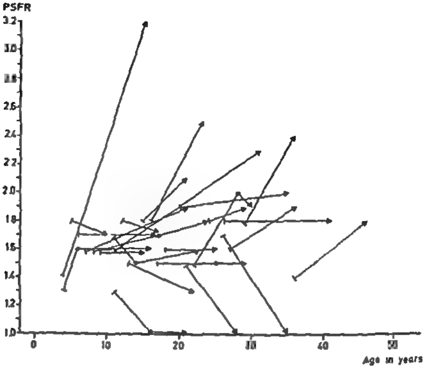

Fig 2 The PSFR and the age at initial and last study in 26 patients with serial heart catheterizations.

Table I Distribution of patients according to initial pulmonary to systemic flow ratio and findings by roentgenograms of the chest and ECG

PSFR	Cardiothoracic index				Prom pulm artery segm	Increased pulm. vasc markings	ECG				Incidence of [illegible] catheterization
	< 0 51	0 51 0 55	0 56 0 60	> 0 60			Normal	RVA	RVH	RBBB	
1 3	4	0	0	0	2/4	0/4	4	0	0	0	1/4
1 4	3	0	0	1	0/4	0/4	0	2	2	0	2/4
1.5	2	2	2	0	1/6	0/6	2	[illegible]	1	1	5/6
1 6	5	2	2	0	3/9	0/9	1	4	2	2	[illegible]/9
1 7	1	1	1	0	1/3	1/3	2	1	1	0	[illegible]/4
1.8	7	2	1	0	3/10	1/10	0	7	1	2	8/10
1 9	1	0	0	0	0/1	0/1	0	0	1	1	1/2
1 3 1 9	23	7	6	1	10/37	2/37	9	16	8	6	[illegible]6/39

RVA, right ventricular axis (frontal QRS axis > 90) RVH RVA + R or R > 0 5 mV in V RBBB QRS > 0 12 sec + R > R in V

One patient deserves special comment as the PSFR increased from 1 4 to 3 [illegible] (case 2) At the initial examination in 1952, at the age of 4 years the patient complained of slight dyspnea At auscultation a systolic murmur was heard at the upper left sternal border, but no diastolic murmur was found No evidence of heart failure was found The ECG showed a QRS axis of 120° and in V_1 an R' wave of 7 mm and a negative T wave The roentgenogram of the chest showed a considerably enlarged heart shadow (cardiothoracic index being 0 82) without prominence of the pulmonary artery segment or increased vascular markings At right heart catheterization the PSFR was found to be 1 4 the pulmonary artery pressure 23/6 mm Hg and the mean right pressure 1 mm Hg the right atrium was noted t[illegible] be unusually large In 1963 at the age of 15 [illegible] follow up study was carried out Clinically the condition was unchanged At recatheterization however the PSFR was found to be 3 2, the pulmonary artery pressure 29/13 mm Hg, and the mean right atrial pressure 7 mm Hg The same year operation was performed with extracorporeal circulation and a defect with a diameter of 3 cm was found proximally in the upper part of the interatrial septum The right atrium was huge The defect was sutured and a plastic operation aimed at reducing the size of the right atrium was carried out Later ventricular fibrilla

occurred and the patient died despite at
ɔts at resuscitation At autopsy the right
ricle was found to be enlarged no evidence of
plicating heart diseases such as mitral
osis or tricuspid valve disease were found
ological examination of the right atrial wall
aled hypertrophy of the musculature and
fibrosis of the endocardium

ussion

'he natural history of ASD is only incomplete nown mainly because surgical closure of ASD ame possible at the same time as diagnosis by rt catheterization Comparing the age distri ɿon of ASD patients to that of normal sub ts, Craig and Selzer[4] found a relative decrease the number of ASD patients above 50 years nilar findings were made by Humbert and ociates Campbell found that the mean age at ıth was 37 5 ± 4 5 years of life

These prognostic studies were primarily or lusively dealing with large ASD s It would be ısonable to expect a better prognosis in patients th a small ASD Clinical follow up studies in ese patients are however few In the follow up ıdy of Zaver and Nadas only one child had a ry small ASD (PSFR 1 5) during the 9 years of llow up his ECG remained normal and his ra ological severity grading showed a +1 (out of 4) crease In the same study 10 children had ıtially a PSFR of 1 5 to 3 0 during the follow up riod of 1 10 years the ECG severity grading icreased 0 6 grades (out of 4) with a range of −2) +2 the radiological severity grading showed icreases as well as decreases Among our 39 atients covering a wide range in ages no vidence of clinical deterioration was found

Hemodynamic recatheterization studies in ıfants have shown that spontaneous closure of n ASD of the secundum type may occur[*] hus Mody found that in three out of four nfants having a PSFR of 1 3 to 2 0 the ASD losed spontaneously as it did in eight of 16 nfants having a PSFR higher than 2 0

Follow up hemodynamic examinations are few in patients with small ASD s who are at the initial examination above 1 year of age Zaver and Nadas reported serial heart catheterizations in two patients with a follow up period of 2 and 4 years respectively in one case the PSFR changed from 1.5 to 2 0 and in the other the PSFR changed from 1 9 to 3 0 No change in the pulmonary artery pressure was found Hartmann and Elliott reported a case in which an ASD with a PSFR of 2 5 was demonstrated at the age of 18 months at recatheterization 3 years later the ASD was found to be closed Cumming[11] similarly described functional closure of an ASD with a PSFR of 2 0 during the follow up period from the

Table II Roentgenological examination of the chest Comparison between findings at initial examination and at follow up examination in 20 patients

Study	*Cardiothoracic index* < 0.51	0.51 0.55	0.56-0.60	*Prom pulm artery segment*	*Increased pulmonary vascular markings*
1	11	6	3	6/20	2/20
2	[illegible]	4	3	5/20	2/20

Table III Serial heart catheterization data in 26 cases (mm Hg)

Case No	*Age (yr)* Study 1	Study 2	*PFSR* Study 1	Study 2	*RAMP** Study 1	Study 2	*PA P** Study 1	Study 2
1	11	21	1.3	< 1.3	3	0	30/16	22/11
2	4	15	1 4	3.2	1	7	23/6	29/13
3	36	46	1 4	1.8	4	5	20/7	34/12
4	17	29	1.5	1.5	0	7	15/8	32/12
5	14	23	1.5	1 6	6	3	30/11	27/10
6	13	22	1.5	1.3	2	5	21/7	32/12
7	22	30	1.5	1.9	[illegible]	3	29/15	20/7
8	21	[illegible]	1.5	< 1.3	4	4	22/10	24/9
9	27	36	1 6	1.9	[illegible]	10	31/12	30/9
10	11	31	1 6	2.3	3	3	26/8	28/11
11	7	21	1 6	1.9	3	3	29/8	20/6
12	8	[illegible]	1 6	1.8	0	3	13/7	24/7
[illegible]	4	16	1.6	1 6	3	4	18/7	27/8
14	18	25	1 6	1 6	4	2	25/8	25/10
15	9	15	1.6	1 6	2	4	20/6	25/10
16	6	17	1 7	1 7	4	6	29/16	31/12
17	28	35	1 7	< 1.3	3	2	23/10	20/6
18	23	38	1.8	1.9	5	4	[illegible]	20/6
19	26	41	1.8	1.8	3	3	[illegible]	19/7
20	5	10	1.8	1 7	1	1	21/5	31/7
21	29	36	1 8	2.4	4	3	22/11	31/9
22	24	29	[illegible]	1.9	2	4	19/9	24/6
23	16	23	1.8	2.5	4	7	25/9	27/10
24	15	21	1.8	2.1	3	4	32/10	29/11
[illegible]	12	17	1.8	1 7	1	2	25/6	22/6
26	20	35	1.9	2.0	2	5	22/8	20/10

RAMP right atrial mean pressure PA P pulmonary artery pressure.

age of 2 to 8 Mody[13] found that the PSFR remained unchanged in two patients who initially had a PSFR of 1.5 and 2.0, respectively, the follow up periods were 1½ and 14 years, respectively

Among our 26 patients the PSFR remained small or showed only insignificant changes in 22 patients, in three of them (cases 1 8 and 17) the left to right shunt could be detected only with the hydrogen test at recatheterization but not by blood oxygen examination, in 17 cases the PSFR remained within the original range of 1.3 to 1.9 whereas the PSFR value in two patients (cases 24 and 26) was 2.1 and 2.0, respectively thus now exceeding our initial criteria for a small ASD

In the four remaining patients (cases 2 10, 21, and 23) significant increases in PSFR occurred, but no changes were found in symptoms ECG, or roentgenograms of the chest All four patients did at recatheterization have a large' ASD according to our definition the initial PSFR was 1.4, 1.6, 1.8 and 1.8 respectively Patient 2 has been discussed in detail above, the huge right atrium found at operation might represent a special anomaly or an error might have been present at the initial examination, although we have not been able to find it Nakamura and associates[14] described a similar case in which the PSFR changed from 1.3 in infancy to 3.6 at re examination 5 years later, these authors felt that the result of the initial examination possibly had been incorrect as the PSFR was calculated on the basis of only one sample from the pulmonary artery

The over all picture of increases and decreases in PSFR as seen from Fig 2 is in accordance with the large standard deviations of PSFR determination described in Methods' and is similar to the findings of Zaver and Nadas[9] in their recatheterization study of 13 patients (1.5 to 5.0 to 2.0 1.9 to 3.0, 2.0 to 2.0, 2.0 to 4.0, 2.5 to 2.5 2.5 to 2.5 2.5 to 3.5 2.5 to 4.0, 3.0 to 2.5, 3.0 to 4.0 3.0 to 5.0 >4 to 3.0, and >4 to >4)

Our experience with 26 patients regarding the natural history of small ASD s may thus be summarized whereas no changes occur in most of the patients, a few may very well show a significant increase in PSFR thereby exceeding the limit between small and large ASD s of a PSFR ≥ 2.0 hitherto used in this hospital

Our conclusion as to operative treatment is similar to that of Nadas and Fyler[4] and Moss and Siassi[1] in that we will continue to recommend operation in patients with large ASD s, wh... we still do not consider patients with small AS... candidates for surgery, however we will fol... the latter patients for longer periods to en... that no deterioration occurs and to extend... knowledge of the natural history

Because of the inaccuracy of PSFR determ... tion, the decision as to whether an ASD is to... regarded as large or small will not be based... chosen limit of PSFR ≥ 2.0 alone, we will... take other factors into consideration such as t... presence or absence of diastolic flow murmu... ECG changes, heart enlargement, and increas... pulmonary vascular markings

Summary

Thirty nine patients with a small ASD of secundum type were followed clinically for 5 ... years (mean 11.[illegible] years), no evidence of de... tion was found In 26 of these cases ... tion was carried out with a mean follow up peri... of 9.8 years No significant changes were ... most patients in four patients however the le... to right shunt had increased significantly O... recommendations are that we will continue t... advise surgery in patients with large ASDs whereas we still do not recommend surgery ... patients with small ASD s, the latter patie... should be followed for longer periods to ensur... that no deterioration occurs The decision as to whether an ASD should be regarded as large o... small in our opinion not only should be based on ... chosen limit of pulmonary to systemic flow ratio but clinical factors such as diastolic flow murmurs ECG changes, the heart size, and the pulmonary vascular markings should also be taken into consideration

REFERENCES

1 Moss A J and Siassi B The small atrial sept... defect—operate or procrastinate? J Pediatr 79 ... 1971

2 Hager W Hamodynamik und Klinik des Vorhofsep... tumdefectes Munch Med Wochenschr 111 931 1969

3 Gasul B M Arcilla R A and Lev M Heart disease ... children Philadelphia 1966 J B Lippincott Company p 390

4 Nadas A S and Fyler D C Pediatric cardiol... Philadelphia 1972 W B Saunders Company p 333

5 Sandøe F Congenital isolated ventricular septal defect Thesis Copenhagen 1963 p 26

6 Craig R J and Selzer A Natural history and progn... of atrial septal defect Circulation 37 805 1968

7 Humbert J Renais J Garcia Moll M Scebat L and Lenègre J Histoire naturelle des communications inter auriculaires, Arch Mal Coeur 58 690 1965

Campbell, M Natural history of atrial septal defect Br Heart J 32 820 [illegible] 0

Zaver A. C and Nadas, A. [illegible] Atrial septal defect—secundum type Circulation 31 32 (Suppl. III) 24 1965

Cayler C. G Spontaneous functional closure of symptomatic atrial septal defects, [illegible] Engl. J Med 276 65 1967

Cumming, G R. Functional closure of atrial septal defects, Am. J Cardiol. 22 888 1968.

Hoffman, J I E Rudolph, A. M., and Danilowicz, D Left to right atrial shunts in infants, Am. J Cardiol. 30 868, 1972.

13. Mody M. R. Serial hemodynamic observations in secundum atrial septal defect with special reference to spontaneous closure Am. J Cardiol. 32 978 19/3.

[illegible] Hartmann, A. F., and Elliott, L. [illegible] Spontaneous physiologic closure of an atrial septal defect after infancy Am. J Cardiol. [illegible] 290 1967

15. Nakamura, [illegible] F., Hauck, A. J., and Nadas, A. [illegible] Atrial septal defect in infants, Pediatrics 34 101 1964

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The over all picture of increases and decreases in PSFR as seen from Fig 2 is in accordance with the large standard deviations of PSFR determination described in 'Methods and is similar to the findings of Zaver and Nadas[8] in their recatheterization study of 13 patients (1 5 to 5 0 to 2 0 1 9 to 3 0, 2 0 to 2 0 2 0 to 4 0, 2 5 to 2 5, 2 5 to 2 5 2 5 to 3 5, 2 5 to 4 0, 3 0 to 2 5, 3 0 to 4 0, 3 0 to 5 0 $>$ 4 to 3 0, and $>$ 4 to $>$ 4)

Our experience with 26 patients regarding the natural history of small ASD s may thus be summarized whereas no changes occur in most of the patients, a few may very well show a significant increase in PSFR thereby exceeding the limit between small and large ASD s of a PSFR $\geq$ 2 0 hitherto used in this hospital

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REFERENCES

1 Moss A J and Siassi B The small atrial sep... defect—operate or procrastinate? J Pediatr 78 ... 1971

2 Hager W Hamodynamik und Klinik des Vorhofsep... tumdefectes Munch Med Wochenschr 111 931 1969

3 Gasul B M Arcilla R A and Lev M Heart disease in children Philadelphia 1966 J B Lippincott Compan... p 390

4 Nadas A S and Fyler D C Pediatric cardiol... Philadelphia 1972 W B Saunders Company p ...33

5 Sandøe L Congenital isolated ventricular septal defect Thesis Copenhagen 1963 p 26

6 Craig R J and Selzer A Natural history and prognosis of atrial septal defect Circulation 37 805 1968

7 Himbert J Renais J Garcia Moll M Scebat L and Lenègre J Histoire naturelle des communications inter auriculaires Arch Mal Coeur 58 690 1965

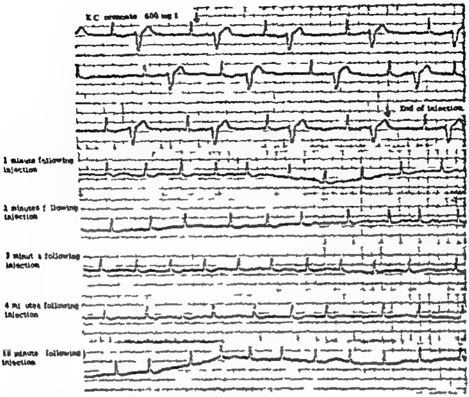

Fig 1 Effect of 400 mg (1 0 mEq) of potassium canrenoate on cardiac rhythm in a 54 year-old patient with rheumatic mitral stenosis, atrial fibrillation, and frequent VPC s thought to be due to excess of digitalis. Note the many long R R intervals (> 1 second) in the control Lead II recording (upper panel) Immediate suppression of VPC s and increases in ventricular rate due to improved A V conduction were evident after potassium canrenoate therapy (lower panel) (Patient 7)

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All 12 patients had severe heart disease and at he time of study were in functional class IIID or VE with seven showing evidence of congestive heart failure Six had atrial fibrillation Seven of he group also had anorexia nausea or vomiting but none complained of yellow or green vision Four (Patients 3 5 6 and 10) had an elevated serum glutamate oxaloacetate transaminase but a normal serum glutamate pyruvate transaminase only Patient 10 had a clinical diagnosis of an acute myocardial infarction All were normokalemic and normocalcemic None showed advanced renal impairment (BUN < 40 mg per 100 ml.) Four (Patients 1 3 8 and 9) were in metabolic alkalosis (pH 7.52 to 7 60) and one had respiratory acidosis (Patient 11 pH 7 29)

ght of the 12 patients who received a mean dose of 525 mg (1.31 mEq) of potassium canrenoate the ventricular arrhythmias which were thought to be due to digitalis toxicity were immediately suppressed. The antiarrhythmic effect of the drug lasted from several minutes to a few hours. In one patient (Patient 10) normal sinus rhythm was maintained for up to 4 hours *after* the administration of potassium canrenoate Responses to treatment with the latter are also summarized in Table I Figs. 1 2 and 3 illustrate results obtained from Patients 7 8 and 10 respectively

Even though PVC s were suppressed by potassium canrenoate therapy Patient 6 a 69 year old woman who had suffered rheumatic heart disease more than five decades died of chronic severe heart failure 12 hours after potassium canrenoate administration Patient 11 whose ventricular bigeminy also responded to potassium canrenoate died of respiratory failure 3 days after the clinical trial

Potassium canrenoate did not significantly

Antiarrhythmic activity of potassium canrenoate in man

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Previous work from our laboratories together with that of others has shown that the potassium or sodium salt of the steroid canrenoate, a specific aldosterone antagonist[1] claimed to have a natriuretic and diuretic potency comparable to that of the thiazides,[2,3] reverses acute as well as chronic electrophysiologic manifestations of cardiac glycoside intoxication both in vitro and in vivo in experimental animals[4-15] It has been previously shown that the reversal of cardiac glycoside toxicity by canrenoate had to be mediated by a very specific and yet unclarified molecular mechanism because the drug was ineffective against cardiac arrhythmias induced by norepinephrine acute myocardial infarction, strontium, and barium[7] The present study was undertaken to evaluate the effect of potassium canrenoate in normal diuretic doses on rhythm disturbances in patients thought to exhibit clinical manifestations of digitalis intoxication

Methods

Twelve hospitalized patients between 25 and 69 years of age exhibiting clinical manifestations of digitalis overdose, were studied Pertinent information regarding these patients is shown in Table I Each of our subjects had been on a maintenance dose of one of the digitalis preparations because of heart failure and/or for the control of the ventricular rate in those with atrial fibrillation Diagnoses of digitalis intoxication were made on the basis of a combination of GI symptoms palpitation or skipping of the heart beat laboratory findings of decreased creatinine clearance or elevated BUN and electrocardiographic (ECG) abnormalities of frequent ventricular premature depolarizations (VPCs > 10 per minute Patients 1 7, and 9) and VPCs appearing as bigeminal (Patients 2 3, 4, 5 6 11, and 12) or trigeminal rhythm (Patients 8 and 10) In addition serum digoxin level[16] was obtained in seven patients

After giving informed consent the patients were transferred to coronary care units for a clinical trial of potassium canrenoate with continuous ECG monitoring Blood pressure and rhythm strips were obtained immediately before during and 1 2 3 4 5 and 15 minutes after intravenous administration of potassium canrenoate (mol wt 396 55) 400 to 700 mg (1 to 1 ;0 mEq) Thereafter the patients were followed for up to 4 hours This dosage of potassium canrenoate had previously been recommended for inducing diuresis in patients with fluid and salt retention or secondary hyperaldosteronism[2,3] Since we were investigating only the immediate direct antiarrhythmic activity of the drug no attempt was made to collect 24 hour urine samples for electrolytes and other biochemical studies

Those patients whose ventricular arrhythmias did not respond to potassium canrenoate were subsequently treated with diphenylhydantoin,

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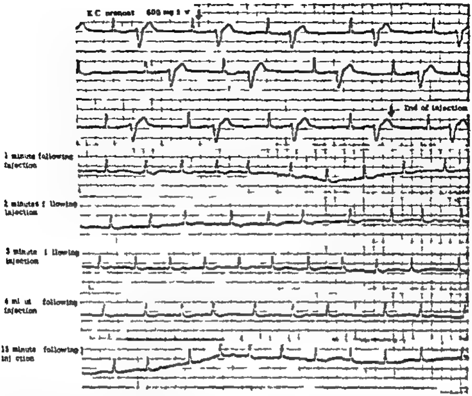

Fig 1 Effect of 400 mg (1.0 mEq) of potassium canrenoate on cardiac rhythm in a 54 year-old patient with rheumatic mitral stenosis, atrial fibrillation and frequent VPC s thought to be due to excess of digitalis Note the many long R R intervals (> 1 second) in the control Lead II recording (upper panel) Immediate suppression of VPC's and increases in ventricular rate due to improved A V conduction were evident after potassium canrenoate therapy (lower panel) (Patient 7)

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In eight of the 12 patients who received a mean dose of 525 mg (1 31 mEq) of potassium canrenoate the ventricular arrhythmias which were thought to be due to digitalis toxicity were immediately suppressed The antiarrhythmic effect of the drug lasted from several minutes to a few hours In one patient (Patient 10) normal sinus rhythm was maintained for up to 4 hours after the administration of potassium canrenoate Responses to treatment with the latter are also summarized in Table I Figs 1 [redacted] and 3 illustrate results obtained from Patients 7 [redacted] and 10 respectively

Even though PVC s were suppressed by potassium canrenoate therapy Patient [redacted] a 69 year old woman who had suffered rheumatic heart disease more than five decades died of chronic severe heart failure 12 hours after potassium canrenoate administration Patient 11 whose ventricular bigeminy also responded to potassium canrenoate died of respiratory failure 6 days after the clinical trial

Potassium canrenoate did not significantly

Table 1 Clinical status and response of patients to potassium canrenoate treatment

Patient	Age	Sex	Digitalis dosage per day	BUN (mg / 100 ml)	Serum K (mEq /l)	Serum digoxin (ng /ml)	GI symp toms	Type of rhythm disturbance	Dosage of po tassium can renoate (mg)	Response to treatment	Cli diagn
1 Q T C	60	F	Digoxin 0 25 mg	27 3	4 3	4 8	Yes	Intermittent SA ar rest with fixed coupling VPC s	500	No	HTCVD with CHF
2 F H	46	M	Digoxin 0 25 mg and 0 125 mg alternate	30 0	4 0	0 7	Yes	AF with bigeminal VPC s	600	Immediate sup pression of VPC s	RHD MS, MI AI, TI with CHF
3 C S W	69	M	Digoxin 0 25 mg	20	4 2	1 7	No	AF with bigeminal VPC s	600	No	ASCVD with CH
4 S Y P	45	M	Unknown	19 5	4 6	2 2	Yes	AF with bigeminal VPC s	500	No	RHD MS MI and AI with CHF
5 H Q C	66	F	Digoxin 0 25 mg	36 0	4 3	3 0	Yes	SR with ventricu lar bigeminy	500	Immediate res toration of NSR	ASCVD with CHF
6 C Y H	69	F	Unknown	19 5	4 5	>1 5	Yes	AF with bigeminal VPC s	500	Immediate sup pression of VPC s	RHD MI, with CHF
7 Y K S	54	M	Powdered digi talis 0 1 Gm	20	–	–	No	AF with frequent VPC s	600	Immediate sup pression of VPC s	RHD MS
8 Y T W	61	M	Digoxin 0 5 mg	21	4 9	2 2	Yes	SR with ventricu lar trigeminy	700	Immediate res toration of NSR	ASCVD with CHF

Abbreviations SA = sinoatrial VPCs = ventricular premature depolarizations AF = atrial fibrillation SR = sinus rhythm HT (CVD) = hyperte sive (cardiovascular disease) ASCVD = atherosclerotic cardiovascular disease CHF = congestive heart failure RHD = rheumatic heart disea MS = mitral stenosis MI = mitral insufficiency AI = aortic insufficiency TI = tricuspid insufficiency COLD = chronic obstructive lung disea and PM = primary myocardiopathy An error was made in the handling of the serum specimen obtained from Patient 6 for digoxin determination th serum digoxin level was reported as > 1 5 ng /ml but the absolute value was not recorded

affect the sino atrial rates regardless of whether the ventricular arrhythmias were suppressed or not Some improvement in cardiac conduction was observed in a few patients with potassium canrenoate therapy (see Fig 1) No deleterious side effects were observed No worsening of con gestive heart failure or significant change in blood pressure were noticed after potassium canrenoate therapy Retching and nausea, which had occurred after intravenous potassium canrenoate in conscious Beagle dogs chronically intoxicated with digoxin, was not observed in our patients

Patients 1, 3, 4, and 9 who did not respond to potassium canrenoate therapy, were treated with parenteral and oral diphenylhydantoin oral po tassium supplement, and temporary withdrawal of digitalis when their clinical status permitted Ventricular arrhythmias completely disappeared in all four patients within 2 to 7 days

Discussion

The present clinical trial of potassium canre noate at a dose level recommended for diuretic therapy showed that the drug is effective against ventricular arrhythmias thought to be due to digitalis toxicity Our results confirm previously published experimental data that canrenoate reverses cardiac glycoside toxicity both in vivo and in vitro[4 6 8 15] even though the specificity of canrenoate s antiarrhythmic activity in man can not be established by the present data Our findings are also consistent with those of Bayle and associates[17] who reported that potassium canrenoate suppresses enhanced ventricular ec

Table I cont d

Patient	Age	Sex	Digitalis dosage per day	BUN (mg / 100 ml)	Serum K (mEq /L)	Serum digoxin (ng /ml)	GI symptoms	Type of rhythm disturbance	Dosage of potassium canrenoate (mg.)	Response to treatment	Clinical diagnosis
M L C.	25	F	Digitoxin 0 1 mg	18	4.5	—	Yes	AF with frequent VPC s	600	No	RHD MS, MI
D C F	46	M	Digoxin 0.25 mg	22.5	3 9	—	No	SR with ventricular (or junctional) trigeminy	400	Immediate restoration of NSR	HT and ASCVD Acute myoc. infarction
L T C	[illegible]	[illegible]	Digoxin 0.25 mg.	12 6	—	—	No	SR with ventricular bigeminy	400	Immediate restoration of NSR	HTCVD and COLD
Y Y C.	51	[illegible]	Unknown	—	4.5	—	No	SR with ventricular bigeminy	400	Immediate restoration of NSR	PM
Mean	54.5	7M		22.4	4 4	>2 3			525 (1.31 mEq)		
S.D	12.8	5F		6 4	0 3	1.3			96.5		
S.E.	3.5			1.9	0 1	0.5			27.9		

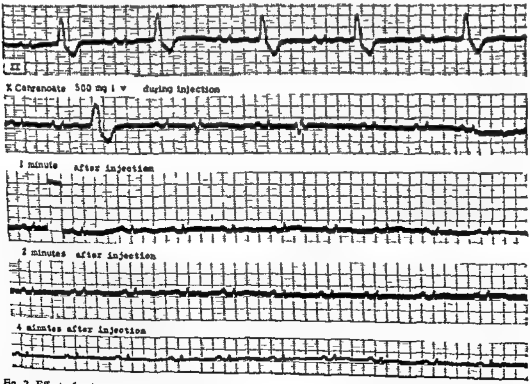

Fig 2 Effect of potassium canrenoate 500 mg (1.25 mEq) on ventricular bigeminal rhythm in a 66-year-old woman with a serum digoxin level of 3 0 ng per milliliter Note that the sinus rate remained unchanged during the restoration of a normal sinus rhythm (Patient 5)

Table I Clinical status and response of patients to potassium canrenoate treatment

Patient	*Age*	*Sex*	*Digitalis dosage per day*	*BUN (mg / 100 ml)*	*Serum K (mEq /l)*	*Serum digoxin (ng /ml)*	*GI symptoms*	*Type of rhythm disturbance*	*Dosage of potassium canrenoate (mg)*	*Response to treatment*	*Cl... diagn...*
1 Q T C	60	F	Digoxin 0 25 mg	27 3	4 3	4 8	Yes	Intermittent SA arrest with fixed coupling VPC s	500	No	HTCVD with Ch
2 F H	46	M	Digoxin 0 25 mg and 0 125 mg alternate	30 0	4 0	0 7	Yes	AF with bigeminal VPC s	600	Immediate suppression of VPC s	PPD M.. MI, AI .. TI with CHF
3 C S W	69	M	Digoxin 0 25 mg	20	4 2	1 7	No	AF with bigeminal VPC s	600	No	ASCVD with Ch
4 S Y P	45	M	Unknown	19 5	4 6	2 2	Yes	AF with bigeminal VPC s	500	No	RHD MS MI, and AI with CHF
5 H Q C	66	F	Digoxin 0 25 mg	36 0	4 3	3 0	Yes	SR with ventricular bigeminy	500	Immediate restoration of NSR	ASCVD with CHF
6 C Y H	69	F	Unknown	19 5	4 5	>1 5	Yes	AF with bigeminal VPC s	500	Immediate suppression of VPC s	RHD MI with CHF
7 Y K S	54	M	Powdered digitalis 0 1 Gm	20	–	–	No	AF with frequent VPC s	600	Immediate suppression of VPC s	RHD MS
8 Y T W	61	M	Digoxin 0 5 mg	21	4 9	2 2	Yes	SR with ventricular trigeminy	700	Immediate restoration of NSR	ASCVD with CHF

Abbreviations SA = sinoatrial VPCs = ventricular premature depolarizations AF = atrial fibrillation SR = sinus rhythm HT (CVD) = hyperten sive (cardiovascular disease) ASCVD = atherosclerotic cardiovascular disease CHF = congestive heart failure RHD = rheumatic heart disea MS = mitral stenosis MI = mitral insufficiency AI = aortic insufficiency TI = tricuspid insufficiency COLD = chronic obstructive lung disea and PM = primary myocardiopathy An error was made in the handling of the serum specimen obtained from Patient 6 for digoxin determination serum digoxin level was reported as > 1 5 ng /ml but the absolute value was not recorded

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…n because of the danger of hyperkalemia Since …er effective modes of therapy for digitalis …uced *arrhythmias* are available we feel that …higher than the conventional diuretic dose of …assium canrenoate should be used in man for …interacting the arrhythmogenic properties of …italis compounds

…Three other potassium sparing diuretics have …o been reported to show some antiarrhythmic …ivity in animal experiments [4,24] but none has …en shown to antagonize clinical arrhythmias in …in Since previously published data indicate …at the antiarrhythmic activity of potassium …nrenoate could not be reproduced by equimolar …otassium chloride and that sodium canrenoate …d essentially similar antiarrhythmic potency …e presently available data indicate that the …nrenoate molecule is the first drug with proved …mbined antiarrhythmic and diuretic activity in …an.

…ummary

The efficacy of potassium canrenoate in suppressing frequent ventricular premature depolarizations and ventricular bigeminal and trigeminal rhythms thought to be due to digitalis overdose was studied in seven men and five women (average age 54 5 years) A mean dose of 525 mg (1.31 mEq) of potassium canrenoate administered intravenously effectively suppressed the ventricular rhythm disturbances in eight of the 12 patients for from several minutes to 4 hours The mean serum digoxin level determined in seven patients was > 2.3 ng per milliliter The ability of potassium canrenoate to counteract digitalis intoxication suggests that the molecule of canrenoate is unique in the clinical setting since it shows both diuretic and antiarrhythmic properties.

REFERENCES

1. Kagawa C M Bouska D J Anderson M L and Krol W F Pharmacological properties of a mineralocorticoid antagonist (SC 14266) Arch Int Pharmacodyn 148 8 1964
2. Gleichmann U Bircks W Bostroem B and Kreuzer H Untersuchungen uber den Einfluss des Aldosteron Antagonisten Aldadiene Kalium auf den sekundaren Aldosteronismus nach Operation mit der Herzlungenmaschine Arzneim Forsch. 17 741 1967
3. Terrasse J and Molnade S Etude des effets diuretiques due 8109 cb dans divers états pathologiques Gaz. Med. Fr 77 130 19 0
4. Yeh, B K., and Sung, P K. Prevention and abolition of ouabain induced ventricular tachycardia by potassium canrenoate in dogs, Eur J Pharmacol.19 151 1972.
5. Yeh, B K., Sung, P K., and Saha A. K Use of potassium canrenoate to suppress ouabain induced ventricular arrhythmias in dogs, Circ. Res. 31 915 1972.
6. Yeh, B K., and Lazzara, R. Reversal of ouabain induced electrophysiological effects of potassium canrenoate in canine Purkinje fibers, Circ. Res. 32 501 1973
7. Yeh, B K., Sung, P K., and Lazzara, R. The specificity of potassium canrenoate—a steroidal antidysrhythmic drug. Clin. Pharmacol. Ther 15 1014 19 4
8. Csapo G Sohn, Y J., and Yeh, B K Electrophysiological effects of potassium canrenoate on ouabain induced ventricular dysrhythmias in rabbits, Pharmacology 11 336, 19 4.
9. De Guzman, N T., and Yeh, B K Potassium canrenoate in the treatment of long term digoxin induced arrhythmias in conscious dogs. Am. J Cardiol. 35 413 1975
10. Lamarche M., and Royer R. Effet d une spironolactone le canrénoate de potassium sur l arythmie de l oreillette isolée induite par un digitalique C R. Soc Biol. Paris 165 1432, 19"2.
11. Pettier H., Hua G., Weiller M and Faivre, G Insuffisance cardiaque chronique et hyperexcitabilité ventriculaire interet d un antialdosterone injectable d action rapide, in Brendel, W., et al., editors Extrarenal activity of aldosterone and its antagonists, Amsterdam 19"2, Excerpta Medica Foundation, pp 101 106.
12. Tournaire, A., and Blum J L'hyperexcitabilité myocardiques des cardiopathies décompensées effets de la spironolactone in Brendel, W et al., editors Extrarenal activity of aldosterone and its antagonists, Amsterdam 1972, Excerpta Medica Foundation, pp. 142 146.
13. Schaumann, W., Koch, K., and Mattern H R Extrarenal actions of aldosterone antagonists in guinea pigs. II. Reduction of the toxicity of β methyldigoxin Arch Pharmacol. 279 9 19 3.
14. Hollander P B Marks, B H and Little W C Electropharmacology of potassium canrenoate Proc Soc. Exp. Biol. Med. 145 710 1974
15. Coraboeuf E., and Deroubaix, E Effect of a spironolactone derivative sodium canrenoate on mechanical and electrical activities of isolated rat myocardium J Pharmacol. Exp. Ther 191 128, 1974
16. Yeh, S. H Lin, I L., Wu H. H., Chien M T and Wang C C Radioimmunoassay for digoxin. I Principle and methodology Chinese Med. J 21 9 1974
17. Bayle, V., Tadei, A. Vernin H., Grimault, Y and Montlahue M. Etude clinique et biologique d une spironolactone injectable le 8109 CB dans les oedemes des cardiaques et des cirrhotiques, Arch. Med de l ouest 2 195 19"0
18. Krämer K. D Vogt, W., Ghabussi, P., and Hochrein H Therapeutischer Wert des Aldosteron Antagonisten Kalium—Canrenoat bei der Digitalis intoxikation Med Welt. 24 462, 19 3
19. Yeh, B K., Sung, P K., Lazzara, R., deGuzman N T Sohn, Y J and Csapo G Reversal of cardiac glycoside toxicity by canrenoate Electrophysiological mechanisms, Circulation 48 (Suppl. IV) 110 1973.
20. Beller G A., Smith, T W Abelman, W H., Haber E., and Wood, W B., Jr Digitalis intoxication A prospective clinical study with serum level correlations, N Engl J Med. 284 989 1971
21. Fogelman A. M., LaMont, J T., Finkelstein S Rado E and Pearce, M L. Fallibility of plasma-digoxin in

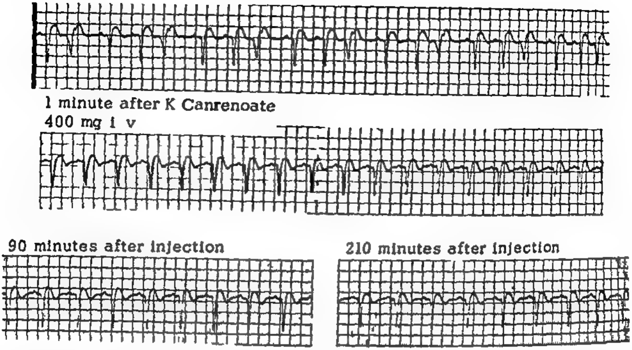

Fig 3 Response to potassium canrenoate 400 mg (1 0 mEq) of a ventricular (or junctional) trigeminal rhythm in a 46 year old man with acute myocardial infarction This patient had been taking a maintenance dose of digoxin, 0 25 mg per day for hypertensive and atherosclerotic cardiovascular disease The sinoatrial cycle length was 577 msec. in the control tracing (top strip monitor lead) During conversion of normal sinus rhythm by potassium canrenoate the cycle length was 615 msec (middle strip) the cycle length gradually increased further and then stabilized at 690 msec Normal sinus rhythm was maintained in this patient for up to 4 hours

topic activity in patients with cardiac arrhythmia Kramer and his associates[18] found little or no improvement in cardiac arrhythmias 24 hours after 600 mg of potassium canrenoate therapy in 10 patients The antiarrhythmic effect of the drug might have dissipated by the time they evaluated their results

Reported electrophysiological mechanisms responsible for the reversal of cardiac glycoside toxicity by canrenoate included restoration of normal automaticity, improvement in conduction, restoration of excitability, and chemical defibrillation [19] The present clinical study suggests that potassium canrenoate as demonstrated in Figs 1 to 3, abolishes digitalis induced ventricular arrhythmias mainly by suppressing the digitalis enhanced ventricular automaticity and/or by improving cardiac conduction but not by sinus 'overdrive'[22]

The serum digoxin level determined in seven patients with presumptive clinical evidence of digitalis toxicity varied from 0 7 to 4 8 ng per milliliter This suggests that a diseased heart may show electrophysiological phenomena consistent with toxicity to therapeutic concentrations of digoxin In other words, consistent with the findings of others, digoxin overdose cannot be established solely on serum digoxin levels alone[20]

Experimental data in vitro indicates that canrenoate has little or no direct inotropic effect and that it does not alter the inotropic response of cardiac muscle to cardiac glycosides It would suggest that the marked depressant effect of the drug reported in isolated guinea pig ventricular myocardium[14] did not occur in man Schroder and associates[21] have previously reported that potassium canrenoate exhibited a positive inotropic effect on the human heart This observation if confirmed by others could add another positive feature to the drug as an antiarrhythmic agent especially in patients with decompensated myocardium

As studies in vitro have shown that potassium canrenoate up to a concentration of 1 mM (400 mg per liter) caused little or no alteration in cardiac mechanical or electrical activity one may be tempted to give higher and repeated doses of the drug in order to obtain better antiarrhythmic results in digitalis intoxication Being also a diuretic agent however, the specific antialdosterone effect of canrenoate on renal tubules necessarily limits the dose that can safely be used in

...perimental and laboratory reports

...fects of hypercapnea and of hypercapnea in ...mbination with hypoxia on midbrain induced ...rdiac dysrhythmias

... Page Mauck, Jr
...fred J Szumski
...mes E Forbes
...artha A. Clendenin
...berta A. Newton
...hmond, Va.

...he frequency with which serious cardiac dys...ythmias occur in patients with acute respira...ory failure has been well documented in recent ...ublications The studies in general have ...own that the rhythm disturbances were asso...iated with moderately severe arterial blood gas ...nd acid base derangement and one report has ...oted in particular that a rapid reversion to a ...ore stable electrical rhythm occurred with ...orrection of the physiological and metabolic ...bnormalities.[1]

Based on experimental studies in the cat ...Mauck and associates[2] have strongly suggested ...hat a dominant factor in both the exhibition and ...everity of cardiac rhythm disturbances observed ...with acute respiratory failure might be the inten...sity of the efferent neural impulse traffic ...manating from high cortical and subcortical regions of the brain Previous studies in the animal have clearly shown that supraventricular and ventricular dysrhythmias may occur with experimental activation of neural regions rostral to the medulla oblongata[3-8] Furthermore in man electrocardiographic (ECG) abnormalities and pathological changes in the myocardium have been observed with cerebral dysfunction due to hemorrhage meningitis and space-occupying lesions[9-10] The anxiety resulting from severe dyspnea and other stress-provoking factors so frequently observed in patients with respiratory insufficiency might be expected to increase significantly autonomic discharge from the cerebral cortex

Acute arterial hypoxia and hypercapnea have been shown in the experimental animal to increase autonomic efferent discharge from neurones residing in subcortical regions of the hypothalamus and mesencephalon and these effects may occur independently of the arterial chemoreceptors[11, 12] Also Szekeres and Papp[13] strongly suggested that the arrhythmias associated with acute arterial hypoxia were mediated through neural mechanisms. Although it is clear that hypoxia may lead to a significant increase in cardiac dysrhythmias with mesencephalic stimulation the exact role of acute arterial hypercapnea alone is far less well defined and has been difficult to assess from a clinical standpoint since hypoxia almost invariably coexists with hypercapnea in the patient with respiratory failure Also the effects of hypoxia and hypercapnea in combination at levels most frequently observed in the patient with respiratory insufficiency have not been heretofore studied experimentally The possibility that hypoxia and hypercapnea in combination might summate to further increase efferent autonomic discharge and thus produce more significant effects on heart rhythm and performance than either alone must be strongly considered Therefore studies have been performed to assess the effects of acute arterial hypoxia and hypercapnea in combination and also isolated hypercapnea on the exhibition of

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differentiating toxic from non toxic patients, Lancet 2 727 1971

22. Evered, D C, and Chapman, C Plasma digoxin concentrations and digoxin toxicity in hospital patients Br Heart J 33 540 1971
23. Schroder R Schüren, K P, Biamino G Meyer V and Sádée W Positivinotrope Herzwirkung von Aldadien Kalium (Aldactone pro injectione), Klin Wochenschr 49 1093, 1971
24. Weber D J Intravenous triamterene in the treatment of acute digitalis intoxication Clin Pharmacol Th[illegible] 13 868 1972
25. de Azevedo I M Dreifus, L S Seller R and C[illegible] Interaction of potassium sparing diuretic amilorde [illegible] digitalis on the heart (abst) Clin Res 21 413, 197[illegible]
26. Yeh B K. Francis J S Jr Gosselin A J and Ela[illegible] A. Antiarrhythmic activity of four pteridine compo[illegible] in ouabain intoxication Clin Pharmacol Ther 17 [illegible] 1975

a II Vagi intact with beta blockade

Cats	Control			Stimulation		
	HR	BP	Rhythm	HR	BP	Rhythm
Room air	14[illegible]	150/80	Sinus	140	1[illegible]5/90	Sinus
Hypoxia and hypercapnea	136	1[illegible]0/80	Sinus	138	160/9[illegible]	Sinus
Room air	160	150/95	Sinus	1[illegible]0	155/100	Sinus
Hypoxia and hypercapnea	158	154/98	Sinus	154	1[illegible]6/100	Sinus
Room air	140	120/80	Sinus	140	130/85	Sinus
Hypoxia and hypercapnea	140	125/85	Sinus	136	135/90	Sinus
Room air	1[illegible]8	11[illegible]/85	Sinus	126	120/85	Sinus
Hypoxia and hypercapnea	130	120/8[illegible]	Sinus	122	130/[illegible]0	Sinus
Room air	16[illegible]	125/8[illegible]	Sinus	164	128/86	Sinus
Hypoxia and hypercapnea	16[illegible]	125/85	Sinus	160	130/[illegible]0	Sinus
Room air	1[illegible]0	110/[illegible]	Sinus	118	110/[illegible]0	Sinus
Hypoxia and hypercapnea	120	112/[illegible]2	Sinus	116	120/80	Sinus
Room air	1[illegible]0	115/60	Sinus	168	120/80	Sinus
Hypoxia and hypercapnea	168	118/82	Sinus	160	130/80	Sinus

...otomy prior to the initiation of all experi-ntal interventions and the procedure was ...rried out in an identical fashion In addition 12 ...imals were studied with an identical experi-ntal design except that 5 per cent CO_2 and ...lance air was used for ventilation to produce ...lated hypercapnea mean P_{CO_2} 54 mm Hg ...ange 50 to 59) and normoxia mean P_{aO_2} 93 ...m Hg (range 89 to 96) Six cats were studied ...llowing bilateral vagotomy Following comple-...on of experiments the brain was perfused with 1 ...r cent potassium ferricyanide and 10 per cent ...rmalin a frozen section was obtained and Nissl ...aining was carried out for identification of the ...ectrode site Electrode placement was verified ...y histological examination Statistical analysis ...f heart rate and blood pressure was carried out ...y means of an analysis of variance the ECG ...hythm disturbances by means of a sign test one ...ided.

Results

In seven cats with intact vagi (Tables I and II) stimulation during ventilation with room air produced a significant increase in heart rate and arterial pressure ($P < 0.01$) but no cardiac dysrhythmias Institution of combined hypoxia and hypercapnea for 10 minutes produced a mild but significant increase in heart rate and arterial pressure ($P < 0.05$) from control levels but failed to elicit any cardiac dysrhythmias Stimulation of the midbrain following 10 minutes of arterial hypoxia and hypercapnea evoked a further significant increase in arterial pressure ($P < 0.01$) and produced serious cardiac rhythm disturbances in all animals ($P < 0.01$) The cardiac dysrhythmias consisted of sinus depression supraventricular tachycardia shifting atrial pacemaker multifocal ventricular premature beats and ventricular tachycardia The rhythm disturbances were observed within 10 seconds of the onset of stimulation in all cats and persisted for 10 to 25 seconds following termination of the stimulus. Following the administration of propranolol stimulation during ventilation with room air failed to produce significant change in heart rate or arterial pressure ($P > 0.05$) or cardiac dysrhythmias Also institution of hypoxia and hypercapnea for 10 minutes produced no significant change in heart rate and arterial pressure from control levels ($P > 0.05$) or cardiac dysrhythmias. Stimulation following the 10 minutes of arterial hypoxia and hypercapnea likewise failed to evoke significant change in heart rate and arterial pressure ($P > 0.05$) or cardiac dysrhythmias Although arterial pressure changes were insignificant a slight increase occurred with stimulation due most likely to persisting peripheral alpha receptor effects (Fig 1) In the seven cats which underwent bilateral vagotomy prior to all experimental interventions (Tables III and IV) stimulation of the mesencephalon during ventilation with room

Table I Vagi intact, without beta receptor blockade

	Cats	Control HR	Control BP	Control Rhythm	Stimulation HR	Stimulation BP	Stimulation Rhythm
1	Room air	176	160/90	Sinus	195	185/110	Sinus
	Hypoxia and hypercapnea	184	175/100	Sinus	205	240/120	Sinus depression multifocal ventricular tachycardia
2	Room air	230	150/100	Sinus	250	200/100	Sinus
	Hypoxia and hypercapnea	255	160/110	Sinus	300	250/130	Multifocal ventricular premature contractions ventricular tachycardia
3	Room air	180	130/90	Sinus	210	190/100	Sinus
	Hypoxia and hypercapnea	185	150/100	Sinus	190	240/115	Sinus pauses, shifting atrial pacemaker ventricular tachycardia
4	Room air	175	140/90	Sinus	190	170/110	Sinus
	Hypoxia and hypercapnea	190	150/100	Sinus	200	160/115	Rapid junctional tachycardia multifocal ventricular premature contractions
5	Room air	185	130/80	Sinus	210	180/115	Sinus
	Hypoxia and hypercapnea	200	135/110	Sinus	220	190/120	Multifocal ventricular premature contractions
6	Room air	160	135/85	Sinus	185	165/100	Sinus
	Hypoxia and hypercapnea	180	160/110	Sinus	190	220/120	Sinus pauses junctional or ventricular tachycardia
7	Room air	210	175/100	Sinus	220	190/110	Sinus
	Hypoxia and hypercapnea	220	180/100	Sinus	230	220/100	Sinus depression, shifting atrial pacemaker multifocal ventricular premature contractions.

cardiac dysrhythmias following midbrain stimulation A comparison of the results has been made with our previous studies in which cardiac dysrhythmias were evoked with acute isolated arterial hypoxia [6]

Methods

Twenty six cats were anesthetized with alpha chlorolose, 30 to 40 mg per kilogram, and ventilation was paralyzed with decamethonium bromide Respiration was controlled with a small animal respirator, and end tidal CO_2 continuously monitored with a Beckman CO_2 analyzer The respiration was controlled to maintain constant eucapnea Stainless steel electrodes, 0 5 mm at the tip, were guided stereotaxically into regions of the mesencephalon known from earlier studies to evoke strong autonomic discharge (coordinates A 3 0, L 1 5, S +1) [14, 15] ECG standard Lead II and arterial pressure were continuously monitored on a Sanborn recorder A Nuclear Chicago constant current stimulator (stimulus parameters duration 0 2 sec, 60 cycles per second, 0 6 to 1 0 milliamps for 10 seconds) was used to evoke an electrical stimulus of sufficient intensity to produce a mild increase in heart rate and arterial pressure The site and intensity of stimulation were maintained unchanged for all subsequent neural activation throughout the entire experimental period Following these initial interventions, arterial blood gases were obtained and a stimulus was delivered during ventilation of the animal with room air, mean Pa_{O_2} 91 mm Hg (range, 85 to 96) and mean Pa_{CO_2} 38 mm Hg (range 36 to 42) In 14 cats the arterial P_{O_2} was then lowered and arterial Pa_{CO_2} elevated by breathing a gas mixture containing 10 per cent oxygen and 5 per cent CO_2 for 10 minutes mean Pa_{O_2} 40 mm Hg (range, 36 to 44) and mean Pa_{CO_2} 55 mm Hg (range 51 to 61) Arterial gases were again obtained and the stimulus was repeated. Following these procedures, the animal was ventilated with room air for 20 minutes Propranolol was administered (0 5 to 1 0 mg per kilogram intravenously) and the electrical stimulus again delivered on room air and with arterial hypoxia and hypercapnea as in the earlier part of the experiment Seven animals underwent bilateral

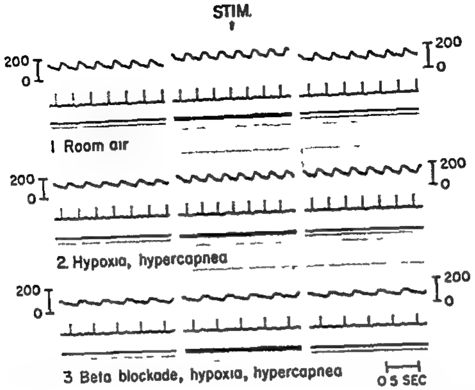

Fig 2. Typical experiment in a cat with bilateral vagotomy Upper panel shows mild increase in heart rate and arterial pressure with stimulation and return toward control 10 seconds following cessation of the stimulus with room air Middle three panels show increase in heart rate and arterial pressure but no cardiac dysrhythmias with stimulation and return toward control levels 15 seconds following cessation of the stimulus with arterial hypoxia and hypercapnea Lower three panels show lower control heart rate following beta blockade with propranolol and arterial hypoxia and hypercapnea, and no change in heart rate or arterial pressure with stimulation.

ır evoked a significant increase in heart rate and rterial pressure ($P < 0\,01$) but no cardiac dys hythmias. Institution of hypoxia and hyper apnea produced a significant increase in heart and arterial pressure ($P < 0\,05$) but no ardiac dysrhythmias Stimulation following 10 minutes of arterial hypoxia and hypercapnea produced a further significant increase in heart rate and arterial pressure ($P < 0\,01$) but only a single ventricular premature contraction in one animal ($P > 0\,05$) Following beta receptor blockade with propranolol stimulation during room air evoked no significant change in heart rate or arterial pressure ($P > 0\,05$) and no cardiac dysrhythmias. Furthermore institution of hypox ia and hypercapnea elicited no significant increase in heart rate or blood pressure ($P > 0\,05$) or cardiac dysrhythmias and stimulation during hypoxia and hypercapnea likewise produced no significant increase in heart rate or arterial pres sure ($P > 0\,05$) and failed to evoke cardiac dys rhythmias. A mild increase in arterial pressure was noted with stimulation both during ventila tion with room air and combined arterial hypoxia and hypercapnea due most likely to persisting alpha receptor effects, but the changes were not statistically significant ($P > 0\,05$) (Fig. 2)

In six animals (Table V) with vagi intact stimulation of the midbrain during ventilation produced a significant increase in heart rate and blood pressure ($P < 0\,01$) but no cardiac dys rhythmias. Institution of mild isolated hyper capnea increased heart rate and arterial pressure ($P < 0\,01$) but induced no cardiac dysrhythmias Stimulation with hypercapnea evoked a further significant increase in heart rate and arterial pressure ($P < 0\,01$) but produced no cardiac dys rhythmias. Beta receptor blockade with propra nolol abolished the increase in heart rate to mild hypercapnea and midbrain stimulation under these conditions ($P > 0\,05$) and attenuated the blood pressure response No cardiac dysrhyth

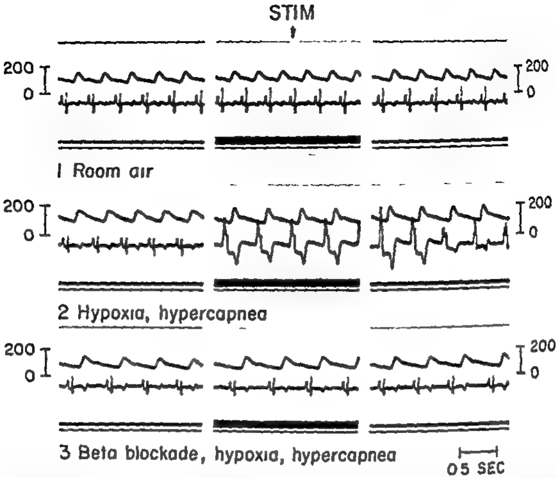

Fig 1 Typical experiment in a cat with the vagi intact Upper three panels show increase in heart rate and blood pressure with return toward control levels 15 seconds after cessation of stimulus with room air Middle three panels show ectopic ventricular rhythm with stimulation and persisting dysrhythmias 10 seconds after cessation of stimulus with arterial hypoxia and hypercapnea Lower three panels show lower control heart rate after beta blockade with propranolol and arterial hypoxia and hypercapnea minimal elevation of arterial pressure and slowing of heart rate during stimulation without dysrhythmias and return toward normal 10 seconds after cessation of stimulation

Table III Vagotomized without beta blockade

		Control			Stimulation		
	Cats	HR	BP	Rhythm	HR	BP	Rh[illegible]
1	Room air	184	150/100	Sinus	200	170/115	[illegible]
	Hypoxia and hypercapnea	190	160/110	Sinus	210	190/120	[illegible]
2	Room air	176	140/90	Sinus	190	150/100	[illegible]
	Hypoxia and hypercapnea	184	144/94	Sinus	210	170/110	[illegible]
3	Room air	168	130/90	Sinus	180	150/110	[illegible]
	Hypoxia and hypercapnea	170	135/95	Sinus	184	160/110	[illegible]
4	Room air	210	150/80	Sinus	230	150/100	[illegible]
	Hypoxia and hypercapnea	220	125/80	Sinus	260	155/110	[illegible]
5	Room air	240	180/120	Sinus	285	220/130	[illegible]
	Hypoxia and hypercapnea	250	180/120	Sinus	310	270/140	[illegible]
6	Room air	220	170/100	Sinus	245	190/110	[illegible]
	Hypoxia and hypercapnea	230	175/100	Sinus	250	190/110	[illegible]
7	Room air	200	160/100	Sinus	230	180/110	[illegible]
	Hypoxia and hypercapnea	230	170/110	Sinus	2[illegible]0	210/120	[illegible]

e VI Isolated hypercapnea vagotomy

Cats		Control			Stimulation		
		HR	BP	Rhythm	HR	BP	Rhythm
1	Room air	146	120/80	Sinus	146	122/82	Sinus
	Hypercapnea	146	125/80	Sinus	146	130/80	Sinus
2	Room air	132	115/[illegible]5	Sinus	132	1[illegible]0/80	Sinus
	Hypercapnea	132	115/80	Sinus	132	120/80	Sinus
3	Room air	150	120/80	Sinus	1[illegible]0	1[illegible]5/80	Sinus
	Hypercapnea	1[illegible]2	120/80	Sinus	1[illegible]0	125/85	Sinus
4	Room air	1[illegible]6	110/[illegible]0	Sinus	12[illegible]	115/[illegible]0	Sinus
	Hypercapnea	124	115/[illegible]0	Sinus	136	120/80	Sinus
5	Room air	134	1[illegible]0/80	Sinus	132	1[illegible]5/80	Sinus
	Hypercapnea	136	1[illegible]5/80	Sinus	136	125/80	Sinus
6	Room air	1[illegible]8	120/80	Sinus	128	1[illegible]4/82	Sinus
	Hypercapnea	128	1[illegible]0/80	Sinus	128	12[illegible]/82	Sinus
a receptor blockade							
1	Room air	172	135/85	Sinus	185	155/100	Sinus
	Hypercapnea	1[illegible]6	140/90	Sinus	192	160/110	Sinus
2	Room air	190	140/90	Sinus	210	180/110	Sinus
	Hypercapnea	194	1[illegible]0/90	Sinus	220	185/110	Sinus
3	Room air	165	135/85	Sinus	1[illegible]5	150/100	Sinus
	Hypercapnea	168	140/85	Sinus	180	155/110	Sinus
4	Room air	180	130/80	Sinus	200	150/100	Sinus
	Hypercapnea	182	135/8[illegible]	Sinus	210	155/100	Sinus
5	Room air	1[illegible]0	125/80	Sinus	180	130/90	Sinus
	Hypercapnea	170	130/80	Sinus	182	140/[illegible]0	Sinus
6	Room air	195	160/90	Sinus	20[illegible]	1[illegible]0/110	Sinus
	Hypercapnea	198	16[illegible]/95	Sinus	212	180/110	Sinus

ias were observed Following bilateral vagot my in six animals (Table VI) stimulation during entilation with room air produced a significant ncrease in heart rate and arterial pressure P < 0 01) but no cardiac dysrhythmias Institu ion of mild hypercapnea evoked an increase in heart rate and arterial pressure (P < 0 01) Midbrain stimulation following hypercapnea pro duced a further significant increase in heart rate and arterial pressure (P < 0 01) but evoked no cardiac dysrhythmias Beta receptor blockade abolished the increase in heart rate (P > 0 05) to both mild hypercapnea alone and midbrain stimulation during hypercapnea and attenuated the blood increase No cardiac dysrhythmias were observed.

Discussion

Although patients with acute and chronic respiratory failure frequently exhibit severe disturbances in cardiac rhythm the mechanisms involved in their exhibition has not been well defined. Some experimental data are available to indicate that autonomic discharge from the brain is increased with either isolated arterial hypoxia or hypercapnea For example hypoxia and hyper capnea alone may increase sympathetic discharge from neural centers rostral to the medulla oblon gata [11] and Szekeres and Papp[12] have shown that when the cat s brain is perfused with hypoxic blood while the remainder of the body is perfused with normally oxygenated blood the threshold to ventricular fibrillation is markedly decreased Although studies by Rogers and associates showed that the threshold to ventricular fibrilla tion failed to decrease with arterial hypoxia and hypercapnea the level of barbiturate anesthesia and length of the experimental period could have as discussed by the authors attenuated or even abolished neural discharge to the heart Under

Table IV Vagotomized with beta blockade

	Cats	Control HR	Control BP	Control Rhythm	Stimulation HR	Stimulation BP	Stimulation Rhythm
1	Room air	140	125/75	Sinus	140	[illegible]	[illegible]
	Hypoxia and hypercapnea	138	130/75	Sinus	138	132/80	[illegible]
2	Room air	150	130/90	Sinus	150	[illegible]/90	[illegible]
	Hypoxia and hypercapnea	150	140/100	Sinus	148	150/100	[illegible]
3	Room air	130	120/80	Sinus	130	[illegible]	[illegible]
	Hypoxia and hypercapnea	130	125/85	Sinus	128	[illegible]	[illegible]
4	Room air	155	125/90	Sinus	153	150/90	[illegible]
	Hypoxia and hypercapnea	155	125/90	Sinus	155	133/95	[illegible]
5	Room air	164	150/90	Sinus	160	155/70	[illegible]
	Hypoxia and hypercapnea	162	155/90	Sinus	160	[illegible]/90	[illegible]
6	Room air	156	140/90	Sinus	152	144/94	[illegible]
	Hypoxia and hypercapnea	155	145/95	Sinus	153	150/100	[illegible]
7	Room air	150	130/80	Sinus	149	135/85	[illegible]
	Hypoxia and hypercapnea	150	130/80	Sinus	150	140/90	[illegible]

Table V Isolated hypercapnea vagi intact

	Cats	Control HR	Control BP	Control Rhythm	Stimulation HR	Stimulation BP	Stimulation Rhythm
1	Room air	176	150/90	Sinus	186	160/95	Sinus
	Hypercapnea	178	154/92	Sinus	194	200/100	Sinus
2	Room air	184	130/80	Sinus	200	155/100	Sinus
	Hypercapnea	186	135/85	Sinus	210	170/110	Sinus
3	Room air	180	125/80	Sinus	195	140/90	Sinus
	Hypercapnea	182	130/85	Sinus	195	145/95	Sinus
4	Room air	155	125/80	Sinus	165	140/90	Sinus
	Hypercapnea	160	125/85	Sinus	175	140/95	Sinus
5	Room air	175	135/80	Sinus	185	145/90	Sinus
	Hypercapnea	180	135/80	Sinus	190	150/100	Sinus
6	Room air	195	140/80	Sinus	220	155/85	Sinus
	Hypercapnea	210	145/85	Sinus	232	160/90	Sinus
Beta receptor blockade							
1	Room air	144	120/80	Sinus	142	125/85	Sinus
	Hypercapnea	140	125/80	Sinus	140	130/85	Sinus
2	Room air	132	115/75	Sinus	132	120/80	Sinus
	Hypercapnea	130	115/80	Sinus	130	[illegible]/80	Sinus
3	Room air	154	120/80	Sinus	152	125/80	Sinus
	Hypercapnea	152	125/85	Sinus	150	130/90	Sinus
4	Room air	128	112/70	Sinus	128	118/[illegible]	Sinus
	Hypercapnea	128	115/75	Sinus	126	125/[illegible]	Sinus
5	Room air	136	120/80	Sinus	136	[illegible]/80	Sinus
	Hypercapnea	134	120/80	Sinus	132	126/85	Sinus
6	Room air	130	118/74	Sinus	128	[illegible]/60	Sinus
	Hypercapnea	130	124/80	Sinus	130	130/80	Sinus

tudies of Sideris and associates[4] who found serious ventricular dysrhythmias including ricular fibrillation and ventricular tachy ia were usually observed in patients with ratory insufficiency with Po_2 tension de sed to less than 37 mm Hg The relationship ich dysrhythmias to hypercapnea was not defined

imary

imulation of the midbrain during acute bined arterial hypoxia and hypercapnea luces serious cardiac dysrhythmias which are evoked when stimulation is elicited either normal arterial blood gas tensions or with ited mild hypercapnea The cardiac dysrhyth s are mediated by both enhanced sympathetic parasympathetic efferent discharge. The lts support the concept that increased onomic activity in combination with acute rial hypoxia and hypercapnea contribute ificantly to the exhibition of serious cardiac thm disturbances Acute hypoxia appears to the major determinant of such dysrhyth s

ERENCES

Ayres, S. M and Grace, W J Inappropriate ventilation and hypoxemia as causes of cardiac arrhythmias, Am J Med. 46 495 1969

Hudson, L. [illegible] Kurt, T L. Petty T L., and Genton E Arrhythmias associated with acute respiratory failure in patients with chronic airway obstruction, Chest 63 661 1973

Holford, F D and Mithoefer J C Cardiac arrhythmias in hospitalized patients with chronic obstructive pulmonary disease, Am. Rev Resp Dis 108 879 1973

Sideris, [illegible] A., Katsadoros, D P Valianos, G., and Assioura, A. Type of cardiac dysrhythmias in respiratory failure, AM. HEART J 89 32, 1975

5 Mauck, H P Jr., Szumski, A. J., Fu T., Forbes, J E., and Clendenin [illegible] A The effect of acute hypoxia on cardiac dysrhythmias induced by mesencephalic stimulation, AM. HEART J 87 197 1974

6. Porter R. W., Kamikawa, K., and Greenhoot, J H Persistent electrocardiographic abnormalities experimentally induced by stimulation of the brain, AM. HEART J 64 815 1962.

7 Weinberg, S J., and Fuster J M., Electrocardiographic changes produced by localized hypothalamic stimulation, Ann. Intern Med. 53.332, 1960

8. Mauck, H. P., Jr., and Hockman, C H. Central nervous system mechanisms mediating cardiac rate and rhythm, AM HEART J 74:96, 1967

9 Hersch, C Electrocardiographic changes in subarachnoid hemorrhage meningitis and intracranial space occupying lesions, Br Heart J 26 785 1964

10. Connor R. C R. Myocardial damage secondary to brain lesions, AM. HEART J 78 145 1969

11 Downing, S E., and Siegel, J H. Baroreceptor and chemoreceptor influences on sympathetic discharge to the heart, Am. J Physiol. 204 471 1963

12. Downing, S. E., Mitchell, J H., and Wallace A. [illegible] Cardiovascular responses [illegible] ischemia, hypoxia, and hypercapnea of the central nervous system, Am. J Physiol 204 881 1963.

13. Szekeres, L. and Papp G Effect of arterial hypoxia on the susceptibility to arrhythmia of the heart, Acta Physiol. Acad. Sci. Hung. 32 143 1967

14 Snider R. S., and Niemer W T A stereotaxic atlas of the cat brain, Chicago 1961 University of Chicago Press.

15 Hockman, C H., Mauck, H P., Jr., and Hoff E C., ECG changes resulting from cerebral stimulation II A spectrum of ventricular arrhythmias of sympathetic origin AM. HEART J 71 695 1966.

16 Rogers, R. M., Spear J F., Moore, E. N., Horowitz L. H., and Sonne, J E. Vulnerability of canine ventricle to fibrillation during hypoxia and respiratory acidosis, Chest 63 986, 1973.

17 Hornbein, T [illegible] The relation between stimulus to chemoreceptors and their response in Torrance R. W., editor Arterial Chemoreceptors, Oxford and Edinburgh, 1968 Blackwell Scientific Publications, p 65

these experimental conditions it might be expected that the results would differ significantly from those observed in a lightly anesthetized preparation studied for short experimental periods In the denervated preparation ventricular fibrillation threshold is unchanged with hypoxia [13] Mauck and associates[5] have shown in lightly anesthetized cats that moderate hypoxia enhances the exhibition of cardiac dysrhythmias with midbrain stimulation Thus, some evidence is available to support the concept that acute alterations in arterial blood gases together with enhanced neural discharge may lead to the production of serious cardiac rhythm disturbances

The effect of isolated hypercapnea as a determinant in the production of cardiac dysrhythmias at the clinical level has been difficult to assess as hypoventilation associated with respiratory insufficiency almost invariably produces concomitant severe arterial hypoxia In the studies reported isolated hypercapnea of a degree frequently encountered in patients with mild respiratory insufficiency failed to produce significant changes in cardiac rhythm In contrast when mild hypercapnea was combined with moderate hypoxia serious cardiac dysrhythmias were evoked with central stimulation in all animals studied, and these arrhythmias were totally abolished by interruption of parasympathetic discharge to the heart Beta receptor blockade totally abolished the arrhythmias when the parasympathetic nervous system remained intact Thus, the integrity of both divisions of the autonomic nervous system must be maintained in order that rhythm disturbances be produced with combined hypoxia and hypercapnea The results differ significantly from earlier reported studies performed during isolated hypoxia and maintained eucapnea in which cardiac dysrhythmias occurred in only approximately one half of the animals with vagi intact Furthermore these rhythm abnormalities were only mildly attenuated with parasympathetic blockade while total abolition resulted with beta receptor blockade [5] Thus, the current studies strongly suggest that cardiac arrhythmias associated with a combined arterial blood gas abnormality are influenced more predominantly by efferent parasympathetic discharge than when such dysrhythmias occur with isolated hypoxia alone The differences observed might be related to increased activation of arterial chemoreceptors as a res lt of hig carbon dioxide tension Hornbein[11] has de strated that efferent neural impulse traffic f the aortic chemoreceptors is influenced in additive fashion by the combined effect hypoxia and hypercapnea Thus, in the isola perfused carotid body in which neural disch was monitored during changes in Po$_2$ of 40 mm Hg and Pco$_2$ of 35 mm produced only approximately 30 per cent neur discharge, whereas at the same level of hypo with Pco$_2$ increased to 57 mm Hg per ce activation was observed Since it has now be clearly shown by Calaresu that the efferent li of the aortic chemoreceptor is purely parasymp thetic, it appears reasonable that gr influence on heart rhythm would be evoked this latter division of the autonomic system when hypoxia is combined w levels of carbon dioxide tension Other possibi ties might relate to direct effects of carbon dioxi on the myocardium with depression of functi such as to make the heart more susceptible t cardiac rhythm disturbances or possibly altered afferent cardiac vagal impulses due to hypercap nea It is not possible to answer such questio from the experiments as the blood gas distu bances affect simultaneously the entire neur reflex arc as well as the myocardium locally

The studies clearly demonstrate that a combi nation of hypoxia and hypercapnea such as frequently seen in the clinical situation is capable of producing serious cardiac rhythm disturbances when autonomic efferent discharge is increased by experimental activation of the central nervous system It must be emphasized however, that i ill patients with respiratory insufficiency addi tional abnormalities may be present such pulmonary hypertension and left ventricu dysfunction which could alter the tension of th atrial myocardium and contribute to cardi dysrhythmias Hypoxia and hypercapnea toget er appear to more consistently produce rhyth disturbances than isolated hypoxia with euca nea However mild elevation of the carb dioxide tension alone failed to produce any d turbances in cardiac rhythm under these expe mental conditions Therefore it appears that t decreased arterial oxygen tension is far mo closely related causally to the exhibition serious rhythm disturbance than is carbon dio ide Furthermore this observation is supported

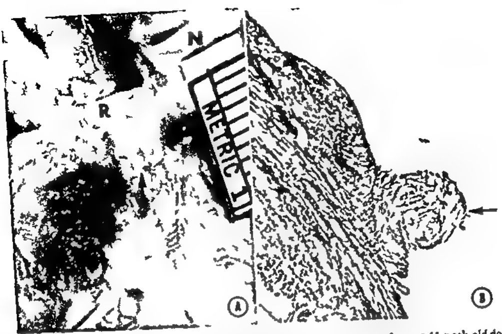

Fig 1 Grade 1 SAS—Newfoundland 151 *A* The left ventricular outflow tract region from an 11 week-old dog with a Grade 1 systolic murmur The aortic cusp adjacent to the rule is the noncoronary cusp (*N*) Below the right coronary cusp of the aortic valve (*R*) are a number of whitish raised nodules (arrow) A nodule can also be seen on the right coronary cusp *B* A section made through the LVOFT and right coronary cusp The arrow points to one of the raised areas seen in *A* These consist of loose fibrous connective tissue covered by endothelium The cells in the nodules are fibroblastic and surrounded by alcian blue positive ground substance intermixed with delicate connective tissue fibrils. The bases of the raised areas contain large numbers of dilated capillaries. (Hematoxylin and eosin × 200)

24 hours before complete dissection The hearts from young pups were examined under a dissecting microscope at 6× to 12× magnifications

Five different types of matings were carried out

1 Affected Newfoundland × affected Newfoundland
2. Affected Newfoundland × normal Newfoundland
3 Affected Newfoundland × normal non Newfoundland (offspring are F generation)
4 F (affected) × affected Newfoundland (F backcross to affected line)
5 F (affected) × normal non Newfoundland (F backcross to normal line)

The chromosomes of three affected dogs were studied with cultured peripheral blood leukocytes Reagents for the procedure were obtained in a commercially available kit * A minimum of 15 metaphase spreads from each dog were photographed and counted and a karyotype of each dog was constructed

Results

Pathology of the stenotic lesion A total of 139 dogs from 22 test matings were studied Of these 42 (30 2 per cent) had one of the forms of SAS described below Two of the 42 had valvar pulmonic stenosis as well as SAS One other dog had isolated valvar pulmonic stenosis For purposes of description and analysis the SAS lesions were classified according to severity as Grades 1 through 3 as follows

Grade 1 SAS This mildest form recognizable by gross examination consisted of a variable number of small (1 to 2 mm) whitish slightly raised nodules on the endocardial surface of the interventricular septum immediately below the aortic valve similar nodules were also seen on the ventral surface of the aortic valve cusps in some animals (Fig 1 *A*) Histological examination of these nodules revealed fibroblastic cells sur

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The genetics and pathology of discrete subaortic stenosis in the Newfoundland dog

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Discrete subaortic stenosis (SAS) is a heart defect common to man,[1] dog,[2] pig,[3] and cow [4] In all of these species, the lesion is described as a ridge or ring of fibrous tissue located in the left ventricular outflow tract (LVOFT) immediately below the aortic valve In man and dog, SAS is usually considered to be a congenital defect which can give rise to various symptoms (e g , angina, sudden death) and clinical signs (e g , systolic murmur, ischemic ECG changes radiographic enlargement of the left ventricle and ascending aorta)

SAS in man is found predominantly in males and is reported to have a multifactorial genetic cause [5] In preliminary genetic studies of the same family of Newfoundland dogs reported in this paper, the results did not differ significantly from those expected with autosomal dominant inheritance but autosomal recessive or more complex modes of inheritance could not be excluded [6] Gross and microscopic pathologic findings in sporadic cases of canine SAS have been reported in breeds other than the Newfoundland,[7] but the full spectrum of lesions within a related group of dogs has not been described

It is the purpose of this paper to present new evidence regarding the mode of inheritance of canine SAS and to more fully describe the range of pathologic findings in this inherited malformation Based on this evidence a hypothesis regarding the underlying genetic abnormality the pathogenesis of SAS will be presented.

Methods

Newfoundland dogs used in breeding experiments were donated by breeders who cooperated in the study Normal non Newfoundland dogs were selected from various purebred lines (black and tan coonhound, malamute, Labrador retriever, boxer, collie) not known to have SAS.

All dogs were housed in runs in climate-controlled rooms Commercial dog food* was fed, beginning at weaning There was no known exposure of females to teratogenic agents and signs of infectious or other diseases were not recognized during pregnancy or the lactation period

Whelping occurred in heated pens The pups were weighed and examined daily for the first 6 weeks, cardiac auscultation was carried out once a week Immunization for canine distemper and infectious canine hepatitis and worming was done at 6 weeks of age Cardiac catheterization including pressure recordings, intracardiac phonocardiography † and angiocardiography were performed on all dogs after 8 weeks of age Following catheterization all dogs that died or were put to death were submitted for complete postmortem examination Hearts were flushed with water through incisions made in both ventricles near the apex of the heart and placed in 10 per cent neutral buffered formalin for a minimum

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*Wayne Meal mixed with water and Ken L Ration canned dog food
†Simultaneous pressure and sound recordings were made with a cathetertip transducer manufactured by Telco Inc Paris, France.

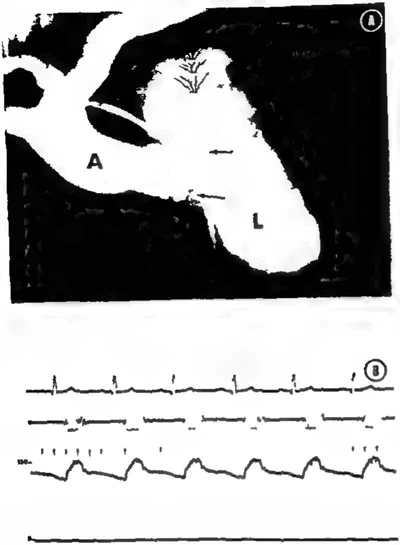

Fig 3 Clinical features of SAS. *A* Angiocardiogram of a male Newfoundland (No 29) that died at 11 years of age with minimal Grade 3 SAS This dog sired many of the dogs included in this study Atrial fibrillation developed at 9 years of age Injection was made in the left ventricle (*L*) The subaortic ring can be seen as a radiolucent line (arrows) in the LVOFT *A* = ascending aorta. *B* From the top Lead [redacted] ECG intra aortic phonocardiogram and pulse curve recorded from the ascending aorta of a 3 month old female Newfoundland (No 39) with a Grade 2 SAS A peak systolic pressure gradient of [redacted] mm Hg was recorded across the LVOFT Note the high amplitude systolic murmur that begins on the serrated ascending limb of the aortic pressure pulse and ends at the dicrotic notch. Time lines at 0 10 sec Phonocardiogram and pressure recordings were made by means of a Dallons Telco catheter tip transducer

iterior leaflet of the mitral valve to the aortic alve The ventricular surfaces of the aortic valve aflets were also thickened (Fig 5 *A*)

The base of the thickened stenotic ring con ained loosely arranged predominantly collage ious fibrous connective tissue with sparse elon ated mesenchymal cells (Figs 4 *B* and 5 *C*) This connective tissue was rich in acid mucopoly saccharides as demonstrated by alcian blue stain ing The mesenchymal cells in the subendocardial region of the stenotic ring had undergone chon drogenic differentiation (Fig [redacted] *D*) The cells in this area were round to polygonal and had a metachromatic capsule when stained with toluid ine blue Some cells were located within lacu nae

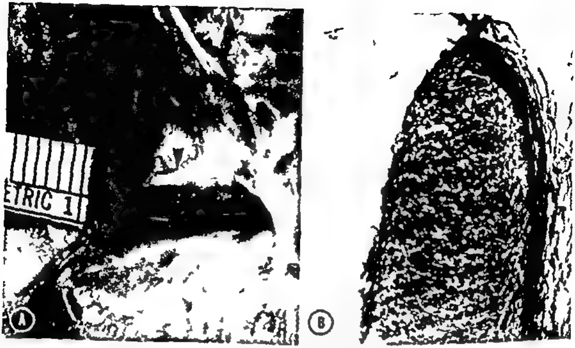

Fig 2 Grade 2 SAS—Newfoundland 305 *A* View of the LVOFT in a 12 week old dog The arrows delineate a fibrous ridge which extends across the *ventricular septum to the left of the anterior mitral leaflet (M) B* Photomicrograph of the fibrous ridge shown in *A* The ridge is covered by endothelial cells and is composed of fibroblastic cells separated by dense collagenous tissue This section was made *at the level of the right coronary* cusp (Hematoxylin and eosin × 230)

rounded by a large amount of delicate connective tissue fibers and alcian blue positive ground substance A large number of endothelium lined spaces and channels which appeared to be either lymphatics or dilated capillaries were present at the base of these nodules (Fig 1, *B*)

Clinical examination of dogs with Grade 1 defects revealed no definite signs of heart disease, although a few had transient, soft, early, systolic murmurs (Grade 1/5) On cardiac catherization, no systolic pressure gradients were recorded across the left ventricular outflow tract and angiocardiograms were normal

Grade 2 SAS In this form, a narrow ridge of whitish, thickened endocardium extended partially around the LVOFT (Fig 2, *A*) The ridge had a variable location, but in most cases originated at the base of the anterior (aortic) leaflet of the mitral valve and extended transversely across the interventricular septum for a variable distance beneath the left coronary cusp of the aortic valve The ridges consisted of fibroblastic cells surrounded by dense collagenous tissue (Fig 2, *B*) Connective tissue fibers appeared much more dense than in Grade 1 defects

Definite clinical evidence of heart disease was not found in any of the dogs with Grade 2 defects All but one, however, were noted to have a short Grade 1 to 2 systolic murmur in the left fourth or fifth intercostal space on one or more examinations In some dogs a murmur heard at one time could not be detected on subsequent examination

On *cardiac catheterization*, most dogs with Grade 2 SAS had no demonstrable systolic pressure *gradient across the LVOFT and* in none did it exceed 20 mm Hg All dogs that had a *as heard by auscultation on the thorax* prior to catheterization had a crescendo descrescendo sys*tolic murmur that was localized to the* left ventricular outflow tract and ascending aorta (*Fig 3 B*) Four dogs that did not *have* detectable murmurs on auscultation of the thorax had an intra aortic murmur in this location Similar murmurs were not found in normal dogs of the same litter

Grade 3 SAS In this most severe form a *fibrous band* ridge, or collar completely *encircled* the left ventricular outflow tract just below the aortic valve The ring was often raised 1 to 2 mm above the endocardial surface and extended *across the interventricular septum* beneath the aortic valve cusp and the anterior leaflet of the mitral valve at its base (Figs 4, *A*, and 5 *A*) In the most severe example a thick endocardial collar extended from the level of the base of the

Table I Results of test matings—Post mortem classification of lesions in offspring

Mating type	No of matings	No of offspring born	No of offspring studied	Age (wk)	Normal	SAS				
						Gd 1 No	Gd 2 No	Gd 3 No	All SAS No	All SAS %
ected × aff Newf	5	30	[illegible]	<3	9	0	0	0	0	0.00
				>3	1†	0	5	9	14	93.33
Total					10	0	5	9	14	58.33
f Newf × norm Newf	3	30	24	<3	15	0	0	[illegible]	0	0.00
				>3	1	0	5	3	8	88.89
Total					16	0	5	3	8	33.33
f Newf × norm non Newf (F)	8	41	40	<3	20	0	0	0	0	0.00
				>3	12	1	4	3	8	40.00
Total					32	1	4	3	8	20.00
ff F × Aff Newf (F backcross to aff)	3	31	31	<3	12	0	0	0	0	0.00
				>3	7	1	8	3	12	63.16
Total					19	1	8	3	12	38.71
ff F × norm. non Newf (F backcross to Norm)	3	20	20	<3	1	0	0	0	0	0.00
				>3	19	0	0	0	0	0.00
Total					20	0	0	0	0	0.00
Total	22	152	139		97	2	22	18	42	30.22

In ea h of these two mating types, a few anim ls were sold by the breed r and n t a ailable for examination. These are excluded from the nalysis.

One dog had valvular pulmonic stenosis but no evide e f SAS

lesions of varying severity according to age (Table II) While a systematic study utilizing post mortem sampling at various age groups was not done it was noted that the mildest lesions described above as Grade 1 SAS were never observed in dogs over 12 weeks of age whereas Grade 3 defects were found predominantly in dogs over 6 months of age This suggests that Grade 1 SAS lesions are an early form of the defect which matures with age

If the incidence of SAS in males vs females is considered for each individual mating class the risk in males was not significantly different than in females ($\chi^2 = 3.59$ df = 3 $P < 0.30$) and the sexes are combined in further analyses

Genetic studies Cytogenetic studies in three dogs with Grade 3 subaortic stenosis revealed a normal modal chromosome number of 78 with normal chromosome morphology as determined in nonbanded karyotypes

Table II Distribution and type of lesion according to age

Age	Grade 1	Grade 2	Grade 3	Normal
0-3 wk.	0	0	0	57
3-6 wk.	0	1	0	2
6-12 wk.	2	5	2	11
[illegible] wk. to 6 mo	0	6	1	16
> 6 mo	0	10	15	11
	2	22	18	97

The results of test matings are given in Table I If all grades of SAS are considered equivalent and all offspring are included in the analysis regardless of age at death the following conclusions can be drawn (1) Autosomal and X linked recessive inheritance are ruled out by the finding that normal offspring resulted from matings between

Fig 4 Grade 3 SAS—Newfoundland 129 *A* Complete fibrous ring from a 2 ½ year old dog with a loud systolic cardiac murmur characteristic of SAS The ring (arrows) completely encircles the LVOFT Part of the anterior mitral leaflet (M) near its mural attachment is discretely thickened and accounts for part of the ring. Part of the aortic valve can be seen beyond the ring *B* Low power photomicrograph of the fibrous ring shown in *A* The ring consists of swirls of fibrous tissue arranged in various directions The superficial region of the ring contains dense collagenous fibrous tissue (single arrow) intermixed with cartilagenous tissue (double arrow) The cartilagenous tissue consists of round or polygonal cells sometimes located in lacunae separated by homogeneous metachromatic mucopolysaccharide matrix (see Fig 5 *D*) (Toluidine blue × 125)

The 18 dogs in this group had Grade 3 4/5 systolic murmurs loudest in the left fourth to fifth intercostal space, but well transmitted to the carotid arteries at the thoracic inlet Electrocardiographic changes included ventricular premature beats (three dogs) atrial fibrillation (four dogs), and high amplitude QRS complexes in Lead II indicative of left ventricular hypertrophy (three dogs)[9] Poststenotic dilatation of the ascending aorta was the most common radiographic finding (seven dogs)

On cardiac catheterization dogs in this group had systolic pressure gradients across the left ventricular outflow tract of 36 to 95 mm Hg and high amplitude systolic murmurs in the left ventricular outflow tract and ascending aorta Angiocardiography demonstrated narrowing of the left ventricular outflow tract including visualization of a discrete subvalvular ring poststenotic dilatation of the ascending aorta, and left ventricular hypertrophy (Fig 3, *A*)

Sudden death has been observed six times in related Newfoundlands with Grade 3 SAS, but only one of these dogs is included in the offspring of the genetic studies described in this paper

Associated myocardial and coronary lesions Dogs with Grade 3 SAS had pathologic changes the left ventricular myocardium These consi… of focal areas of myocardial necrosis and fibro… involving the inner one half of the left ventr… wall (Fig 6 *A*) The myocardial lesions w… accompanied by thickening of the intramyocardial coronary arteries due to fibromuscular proliferation and an increased amount of connective tissue and ground substance in the med… (Fig 6 *B*)

Age and sex distribution of lesions Althou… 57 of the 139 dogs studied died or were put to death before 3 weeks of age (Table I) in no case was a SAS lesion of any type seen in this group The youngest dog with a detectable lesion was … days old at the time of death Taking 3 weeks as a dividing point if there were no difference in the probability of SAS in dogs above and below it the observed result would be expected with a probability of less than 0 001 ($\chi^2 = 21\ 19$) This finding suggests that SAS in the Newfoundland is not true congenital defect but develops in the postnatal period Further support for this idea comes from examination of the distribution of SAS

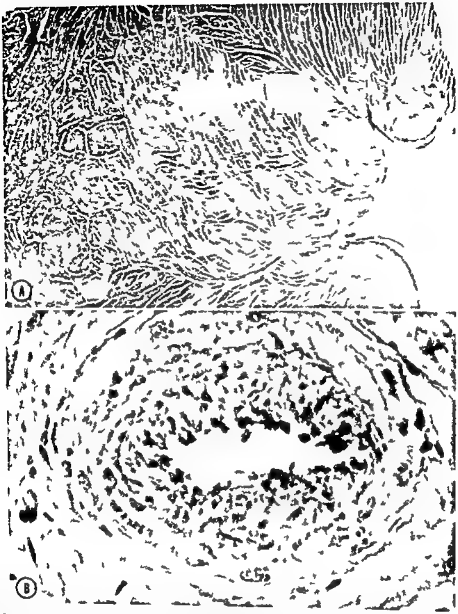

Fig 6 Myocardial and coronary arterial lesions *A* Newfoundland 297 Photomicrograph of the left ventricular myocardium through the anterior papillary muscle The myocardial cells in focal areas in the subendocardial region are replaced by fibrous connective tissue (arrows) (Movat pentachrome × 50) *B* Newfoundland 126. Notice the fibromuscular proliferation in the intima of an intramural coronary artery (Movat pentachrome × 640· oil.)

If we consider the possibility that SAS develops ıstnatally and that pups less than 3 weeks of age ıll not show the gross lesions of SAS regardless their genetic constitution the analysis must be odified Only those dogs that survived longer ıan 3 weeks can be included in the analysis and ıs assumed that those dying before 3 weeks have ıe same probability of SAS as those surviving sing this approach the results of all mating types except the backcross of affected F_1 dogs to normal non Newfoundlands are consistent with autosomal dominant inheritance In the latter matings 20 pups were produced all but one of which lived beyond 3 weeks of age In none of the offspring was a SAS lesion found The probability of such a result under the hypothesis of fully penetrant autosomal dominant inheritance is less than 0 01 (χ^2 = 9 5 df = 1)

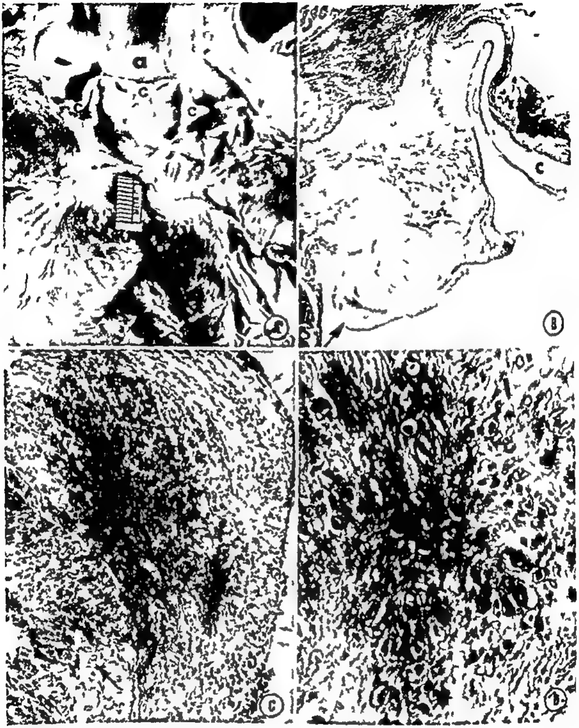

Fig [illegible] Grade 3 SAS–Newfoundland 88 *A* Severe generalized fibrosis of the LVOFT in a 3 month old dog. Immediately above the rule is a prominent band of fibrous tissue It is clear however that the disease process involves the entire LVOFT including the aortic cusps (*c*) as well as the anterior mitral leaflet which is not well seen in this photograph *B* Low power photomicrograph of severe generalized fibrosis of the LVOFT and aortic valve (*c*) The arrow points to a dense band of tissue over the loose connective tissue (Hematoxylin and eosin × 40) *C* Intermediate power photomicrograph of the area beneath the arrow in Fig 5 *B* Notice that the fibrous tissue (thick arrow) is capped by a thick band of cartilagenous tissue (thin arrows) (Movat pentachrome × 125) *D* High power micrograph of the cartilagenous tissue shown in *C* The cells in this region are located in lacunae and are surrounded by highly metachromatic capsules (arrows) The extracellular matrix in this area is also metachromatic (Toluidine blue × 500 oil)

two affected dogs (2) The results of matings between two affected Newfoundlands and matings of affected to normal Newfoundlands did not differ significantly from those expected with fully penetrant autosomal dominant inheritance (3) In outcross (F_1) and backcross matings to normal non Newfoundlands the proportion of affected pups was significantly lower than would be expected under fully penetrant autosomal dominant inheritance ($\chi^2 = 21.58$ df = 2, $P < .001$)

s in the dog do not shed new light on the validity of the theory that the subaortic ring is derived from A V endocardial cushion tissue However while the portion of the ring at the base of the mitral valve might well be derived from A V endocardial cushion tissue it is difficult to explain the septal portion on the same basis If the latter theory is to explain a complete subvalvular ring it is necessary to postulate not only the persistence of A V endocardial cushion tissue but its extension to an abnormal location as well An additional possible explanation for the subvalvular ring is that it is derived from embryonal tissue that at an earlier stage forms the rim of the primary interventricular foramen In horizon XII embryos parts of the rim are formed by endocardial tissue of the crest of the muscular interventricular septum the A V canal cushions and the bulboventricular flange

Regardless of its precise origin our findings strongly suggest that the subaortic ring in discrete SAS represents a persistence of embryonal endocardial tissue in the left ventricular outflow tract this tissue being capable of proliferating and undergoing chondrogenic differentiation after birth The process appears to be controlled by a specific polygenic system or a major gene with modifiers With respect to the frequent occurrence of cartilage formation in the ring it is noteworthy that the fibrous skeleton of the heart including the annulus fibrosis of the aortic valve and the fibrous trigones is a well known site of cartilage formation in the normal dog Thus the embryonal connective tissue of the heart in an area contiguous to the subaortic region does have chondrogenic potential

Summary

Breeding experiments confirm that discrete subaortic stenosis (SAS) in Newfoundland dogs is a specific inherited trait Specificity of the morphogenetic abnormality is not complete however since matings between Newfoundlands with SAS occasionally produced pups with valvular and subvalvular pulmonic stenosis as well as SAS The spectrum of severity of SAS ranged from a subclinical *forme fruste* to a severe form causing death before maturity Well developed subvalvular stenotic rings consisted of a base of loosely arranged fibrous connective tissue and a subendocardial region of cartilagenous tissue Severely affected dogs some of which died suddenly had foci of necrosis and fibrosis in the left ventricular myocardium associated with thickening of the intramural coronary arteries

The lesions of SAS were not found in dogs before 3 weeks of age and the mildest form was seen only in dogs between 3 and 12 weeks of age suggesting that SAS is not a true congenital defect but develops postnatally It is hypothesized that the fibrocartilagenous ring of SAS is derived from persistent embryonal endocardial tissue which retains its proliferative capacity and has chondrogenic potential for some time after birth The results of breeding experiments were not consistent with any simple genetic hypothesis and indicate that SAS is inherited as a polygenic trait or as an autosomal dominant trait with modifiers

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REFERENCES

1 Noth, A M Die subvalvulare Aortenstenose Ergeb Allg Pathol Anat 43 88 1963
2 Detweiler D K The clinical aspects of heart disease in dogs, Vet Scope 1 2, 1955
3 Emsbo P Subaortal stenose Copenhagen, 1955 Dansk Viden Labs Forlag A/S.
4 Jubb K V F and Kennedy P C Pathology of domestic animals, New York 1970 Academic Press Inc., vol 1
5 Jorgensen G Genetische Untersuchungen bei angeborener organischer sub alvularer Aortenstenose Human genetik 7 51 1969
6 Patterson D F Epidemiologic and genetic studies of congenital heart disease in the dog Circ Res 23 171 1968
7 Fluckinger G L and Patterson D F Coronary lesions associated with congenital subaortic stenosis in the dog, J Pathol Bacteriol 93 133 1967
8 Moorhead, P S Nowell, P C Mellman W J., Battips, D M and Hungerford D A. Chromosome preparations of leukocytes cultured from human peripheral blood Exp Cell Res. 20 613 1960
9 Detweiler D K and Patterson D F The prevalence and types of cardiovascular disease in dogs, Ann N Y Acad Sci 127 481 1965
10 Pyle R L, Lowensohn, H S Khouri, E M Gregg, D E and Patterson D F Left circumflex coronary artery hemodynamics in conscious dogs with congenital subaortic stenosis, Circ Res. 33 34 1973
11 Lambert E C Colombi, M Wagner H R., and Vlad P The clinical outlook of congenital aortic stenosis (valvar and discrete subvalvar) prior to surgery *in* Kidd, B S L. and Keith J D editors The natural history and progress in treatment of congenital heart defects Springfield, Ill 1971 Charles C Thomas, Publisher

These results indicate that SAS is not inherited as a simple Mendelian trait, but results from a *polygenic system* or involves a major dominant gene with modifiers The limited data available do *not allow* a distinction between these possibilities

Discussion and conclusions

These studies confirm that discrete SAS is inherited as a specific genetic defect in *Newfoundland* dogs The three dogs with pulmonic stenosis (two with SAS as well) produced in *matings between* dogs with SAS indicate that specificity is not complete, and suggest that the *underlying developmental* abnormality may sometimes extend to the adjacent pulmonary *outflow* tract and valve Pathologic studies show a distribution of severity ranging from subclinical to severe left *ventricular* outflow obstruction that may be lethal before maturity Dogs with incomplete subvalvular rings lacked reliable clinical signs of cardiac disease although low grade systolic murmurs were often present Without a *family* history these would ordinarily be interpreted as innocent murmurs Cardiac catheterization in some cases revealed no systolic pressure gradient across the LVOFT but intracardiac *phono*cardiography demonstrated a systolic murmur localized to the LVOFT and ascending *aorta* suggesting that this could be a useful diagnostic procedure for recognition of the *forme fruste* The sudden death ECG changes and left ventricular myocardial lesions associated with more severe cases of SAS are thought to be manifestations of compromised left ventricular coronary blood flow Recent studies have shown that chronically instrumented dogs with SAS have a left circumflex coronary artery blood flow per gram of myocardium that is below that in normal dogs Furthermore, phasic coronary blood flow is abnormal in that there is marked reversal during ventricular systole [10]

Gross lesions of SAS were absent in pups dying before 3 weeks of age and mild lesions were found only in younger dogs, suggesting that the subaortic stenotic ring develops postnatally It is of interest that no reports could be found of discrete SAS in newborn human infants whereas aortic valvar stenosis of severe degree is well known in this age group and has a high mortality rate [11] A further indication that the subaortic ring may develop postnatally is found in the observa... that hemodynamic and clinical signs in t... human defect frequently indicate progre... obstruction during the first two decades of life

A number of theories have been proposed ... explain the occurrence of fibrous SAS in ma... Keith[12] in 1909 suggested that the ring represe... failure of resorption of a portion of the bulb... cordis Chevers[13] and others[14] believed that th... lesion was caused by repeated infections, prod... ing an inflammatory proliferation of the endoca... dium of the left ventricular outflow tract. Fibr... plaques in the left ventricular outflow tract ha... also been observed in idiopathic hypertroph... SAS in man In this disease, they are attributed t... trauma associated with the impact of the hype... trophied ventricular septum and the anter... leaflet of the mitral valve on each other duri... systole [15, 16] Van Mierop[17] noted that the patho... genesis of fibrous SAS is not clear, but may be associated with malformation of the proxi... extremity of the truncus septum where it join... the conus septum A fifth explanation favored by Van Praagh and associates [18] was first suggeste... by Shaner [19] who noted that fibrous subaorti... stenosis in a pig embryo was associated with malformation of the atrioventricular endoca... cushion surrounding the subaortic left ventric... ular outlet According to this theory, A V cushion tissue in some way impinges on narrows the left ventricular outflow tract

Keith's theory of failure of resorption of ... portion of the bulbus cordis seems to be ruled ou... by indications that the lesion is not a congenital defect but develops postnatally Evi... dence of inflammation is lacking, and the ab... of ventricular hypertrophy in some dogs w... mild SAS lesions mitigates against the hyp... that the ring is associated with primary hyper... tropic myocardiopathy

The present observations do not confirm o... refute the suggestion that the subvalvular ring o... discrete SAS might be derived from embryonic tissue at the junction of the conus and trunc... septum [17] It should be pointed out, however that to explain the portion of the ring at the base of the mitral valve (below the noncoronary cusp of the aortic valve) it is necessary to invoke the possible involvement of the concurrently devel... oping intercalated valve swelling as well as the conotruncal septum proper Likewise, our find

ıtemıc and renal hemodynamıc effects of ııcomıde A new vasodılator

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e synthesıs of hydralazıne by Gross et al[1] ın 0 was wıdely acclaımed as a major advance ın treatment of hypertensıon sınce the drug ered arterıal pressure by reductıon of perıph l vascular resıstance through vascular smooth ıscle relaxatıon whıle at the same tıme ıt lexıvely ıncreased cardıac output and renal ood flow It was soon dıscovered however at hydralazıne was relatıvely weak and ıts olonged use ın large amounts was assocıated th a hıgh ıncıdence of sıde effects ıncludıng lpıtatıons headaches and a syndrome resem ıng systemıc lupus erythematosus There re the use of hydralazıne waned ın favor of the ıbsequently developed sympatholytıc agents ıth the wıdespread use of oral dıuretıcs ɔwever and more recently wıth the avaılabılıty beta adrenergıc receptor ınhıbıtıng drugs hıch serve to prevent the reflexıve cardıac fects ınterest was renewed ın the need for newer nd more potent vasodılatıng compounds havıng ss toxıcıty than hydralazıne The synthesıs and ıbsequent testıng of bupıcomıde a vasodılator avıng antıhypertensıve effects offered such an pportunıty Thıs report detaıls our fındıngs wıth hıs agent upon the systemıc and renal hemody ıamıc functıon ın 10 men wıth uncomplıcated essentıal hypertensıon of mıld to moderate sever ıty

Materıals and methods

Ten male essentıal hypertensıve patıents who were evaluated completely to exclude any second ary forms of hypertensıon were the subjects of thıs study Theır pertınent clınıcal fındıngs are lısted ın Table I All patıents were ınformed about the nature of thıs ınvestıgatıon and formally agreed to partıcıpate ın the study as approved by our Instıtutıonal Human Experımentatıon Commıttee These patıents eıther never receıved antıhypertensıve drugs prıor to evaluatıon or had dıscontınued theır medıcatıons at least 4 weeks before the study

The systemıc hemodynamıc studıes were per formed ın the mornıng after an overnıght fast wıthout premedıcatıon ın a quıet well lıt room wıth the use of prevıously reported technıques In brıef small segments of polyethylene tubıng were ıntroduced ıntravascularly through an ante cubıtal veın and brachıal artery up to the shoulder level by means of the Seldınger[11] tech nıque Thıs enabled contınuous dırect recordıng of arterıal and venous pressures sımulatenously wıth the electrocardıogram (ECG) (Lead II) Control (pretreatment) supıne determınatıons (ın trıplıcate) of cardıac output were obtaıned by ınjectıng 5 mg of ındocyanıne dye followed by a 5 ml salıne bolus flush ınjectıon output determı natıon was repeated after 5 mınutes of 50 degree head up tılt These ındıcator dılutıon curves were replotted semılogarıthmıcally to calculate the mınute output These recorded and calculated hemodynamıc ındıces permıtted calculatıon of

rom the Hypertensı Sect n Departme t of Medıcıne The Unı e ty f Oklahoma Health Sc e ces Ce te and Medıcal Serv ce Veterans Admınıstr tı n Hosp tal, Oklah ma C ty Okla

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12 Keith A Malformations of the heart Lancet 2 359 1909

13 Chevers, N Observations on the diseases of the orifice and valves of the aorta Guy s Hosp Rep 7 387 1842

14 Abbott M E S Atlas of congenital cardiac disease New York 1936 American Heart Association

15 Brachfeld N and Gorlin R Subaortic stenosis A *revised concept of the disease Medicine 38 415 1959*

16 Roberts, W C Pathologic aspects of valvular and subvalvular (discrete and diffuse) aortic stenosis *in* Kidd B S L and Keith J D editors Springfield Ill 1971 Charles C Thomas Publisher

17 Van Mierop L H S Pathology and pathogenesis of the common cardiac malformations *in* Congenital heart disease Cardiovascular Clinics *Philadelphia 1970* F A Davis Company vol 2

18 Van Praagh R Corwin R D., Dahlquist, E H Fe-dom R M Mattioli L. and Nebesar R. A. Tetralogy of Fallot with severe left ventricular outflow [illegible] obstruction due to anomalous attachment of the [illegible] valve to the ventricular septum Am J Cardiol 26 [illegible] 1970

19 Shaner R. F Malformation of the atrioven[illegible] *endocardial cushions of the embryo pig and its rela[illegible]* defects of the conus and truncus arteriosus, Am J [illegible] 84 431 1949

20 Van Mierop L H S Embryology of the heart, *in* Netter F N The Ciba collection of medical illustrations Ciba Vol 5 Heart, Sect. III Summit, N J [illegible] *Ciba Pharmaceutical Company* pp 112 130.

21 *Miller M E Anatomy of the dog* Philadelphia, [illegible] W B Saunders Company, pp 2[illegible]6-2[illegible]7

e II Systemic hemodynamic effects of bupicomide in 10 patients with essential hypertension*

Supine	*Before*	*After*	*p<*
ial pressure (mm. Hg)			
stolic	165 ± 6.8	159 ± 4 3	0 05
astolic	100 ± 2.5	95 ± 3 2	0 05
an	120 ± 4.2	116 ± 3.2	0.05
t rate (b p m)	78 ± 4	88 ± 3	0 025
iac index (ml /min./M)	2 816 ± 184	4,354 ± 154	0 0001
ke index (ml /beat/M)	37 ± 3	50 ± 3	0 005
al peripheral resistance index (mm. Hg/mL/min./M)	0 044 ± 0 002	0 0?7 ± 0 001	0 0001
ventricular ejection rate index (mL/sec./M.)	126 ± 9	163 ± 8	0 005
sion time index (mm./sec./min.)	3 432 ± 148	3,8?5 ± 138	0.005
alva overshoot (% increase diastolic pressure)	34 ± 4	[illegible] ± 5	N.S
PA during tilt (mm Hg)	1.2 ± 3 4	0.3 ± 3.2	N.S
R during tilt (b p.m.)	5 ± 2	11 ± 3	0 05
PRI during tilt (mm. Hg/mL/min /M)	0 007 ± 0 002	0 016 ± 0 008	N.S

h alue represe ts the mean ± S E.M

ole III Renal hemodynamic effects of bupicomide*

	Before	*After*	*p<*
ective renal plasma flow (mL/min)	465 ± 37.8	619 ± 48	0 005
nal blood flow (ml /min)	822 ± 60 3	1 057 ± 80 9	0 001
nal vascular resistance (mm Hg/ml /min)	0 16 ± 0 01	0 12 ± 0 01	0 001
omerular filtration rate (mL/min)	111 ± 8.4	111 ± 6 9	N.S
tration fraction	0.24 ± 0 01	0.18 ± 0 02	0 01
RPF/CI	0 17 ± 0 01	0.14 ± 0 007	025

evised to eliminate decimals.
ch alue represe ts the mean ±1 S E.M

significant decrease in renal vascular resistance ($p < 0\ 001$) (Table III) The glomerular filtration rate remained unchanged however whereas the tration fraction decreased significantly ($p < 0\ 01$) Because the increase in cardiac output exceeded the increase in renal plasma flow the action of blood flow to the kidney actually fell ightly ($p < 0\ 025$) since the glomerular filtra on rate remained unchanged the renal filtration action fell ($p < 0\ 01$)

Clinical effects The only significant side ffects noted during the days of therapy were the ccurrence of headache cutaneous flushing and ardiac palpitations in all patients, especially during the last 2 days of treatment when the igher doses were used Three patients who were not included in this report were removed from the tudy because the headaches and/or palpitations were severe enough to require discontinuation of the medication These side effects disappeared promptly within hours after treatment was with drawn. There were no ECG abnormalities noted during administration of bupicomide or asso ciated with cardiac palpitations and none of the patients complained of precordial chest pain There were no toxic effects of the drug as reflected in the hemogram hepatic or renal func tion tests (Table IV) In accord with changes observed in any hypertensive patient treated with a vasodilating agent plasma volume most likely increased since serum albumin hematocrit and hemoglobin fell slightly but significantly in all patients (Table IV)

Discussion

The results of this study show that when given by mouth, bupicomide was effective in signifi cantly reducing arterial pressure in patients with essential hypertension of mild to moderate sever ity That arterial pressure was reduced by lowering peripheral vascular resistance through a direct arteriolar dilation was demonstrated by the unchanged responses to the Valsalva maneuver and upright tilt and the intact hemodynamic and clinical reflexive changes resulting from arteriolar vasodilation That bupicomide s vasodilating

Table I Admission findings on 10 patients with essential hypertension

Pt	Age (yr)	BP (mm Hg)* Supine	Standing	Fundi KWB	ECG	IVP	BUN mg/100 ml	HHD* class
1	43	175/128	176/139	II	LAD	N	13	II
2	45	168/106	156/109	II	LVH	N	17	II
3	50	14[illegible]/106	149/110	II	WNL	N	19	II
4	[illegible]0	147/99	140/103	II	LAD	N	10	I
5	59	154/106	143/112	I	LVH	N	13	II
6	43	178/105	176/127	II	LAD	N	15	II
7	55	166/108	158/112	I	LAD	N	8	II
8	54	161/103	162/116	I	LAD	N	13	II
9	37	189/128	186/139	II	LVH	N	20	III
10	34	150/06	14[illegible]/10[illegible]	N	WNL	N	12	I

These values represent indirect measurements

total peripheral resistance index by dividing mean arterial pressure by the cardiac index cardiac index by dividing cardiac output by body surface area left ventricular ejection rate index by dividing stroke index by the left ventricular ejection time the ejection time is measured from the upswing of the arterial pressure pulse to the nadir of the incisura in 10 consecutive rapidly (100 mm per second) pulsations and tension time index by multiplying the mean systolic pressure by the injection time divided by the heart rate The above determinations were repeated after 5 days of oral therapy with bupicomide The drug was given every 8 hours as follows the first three doses with 125 mg capsules the next three with 250 mg, the subsequent three with 375 mg, the next three doses with 500 mg and the thirteenth through fifteenth doses with 625 mg capsules After the last dose the patient was brought to the hemodynamic laboratory for repeat studies

Renal function studies were performed on the day prior to the first hemodynamic study and were repeated immediately following the second systemic hemodynamic study These included determination of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) by calculation of the renal clearance of sodium I iothalamate and sodium paraminohippurate respectively Briefly, the patient was given a 'priming' dose of sodium paraminohippurate (PAH) (3 ml 20 per cent solution) with 0 4 ml of I sodium iothalamate (95 μCi), intravenously and was maintained thereafter on a sustaining solution containing 7 ml of PAH and 0 4 ml of I sodium iothalamate in 250 ml of isotonic saline intravenously at a rate of 1 ml per m. (with a pressure independent infusion pump) sample of venous blood was withdrawn before administration of the priming dose for determination of background radiation After an equilibration period of 45 minutes the patient emptied bladder by spontaneous voiding and the urine discarded Thereafter three timed urine collections were obtained at 20 minute intervals instructing the patient to void in the erect position Peripheral venous blood from the opposite arm was drawn between urine collection periods After the third collection period the study was concluded and the clearances of PAH and I sodium iothalamate were determined by methods previously reported[14,15] The results of the clearance determinations were averaged and the mean was taken as the pre or post bupicomide value The renal blood flow (RBF) was calculated from the formula RBF = ERPF × (1/1 Hct) From the RBF, the renal vascular resistance (RVR) in arbitrary units was calculated from the formula RVR = MAP/RBF The systemic and renal hemodynamic data were analyzed statistically by applying Student s t test

Results

Systemic hemodynamic changes Systolic and diastolic arterial pressures were reduced in the 10 patients and mean arterial pressure fell 7 This fall in arterial pressure was significant for the entire group ($p < 0.05$) and was associated with a markedly reduced total peripheral resistance in all 10 patients ($p < 0.001$ Table II) Associated with the fall in vascular resistance and arterial pressure was a significant increase in heart rate ($p < 0.025$) stroke ($p < 0.005$) and cardiac ($p < 0.0001$) indices left ventricular ejection rate index and tension time index ($p < 0.005$) Bupicomide did not interfere with sympathetic nervous system mediated circulatory adjustments as is evidenced by the overshoot of diastolic pressure during the Valsalva maneuver or the changes of mean arterial pressure and total peripheral resistance before and during treatment

Renal hemodynamic changes Associated with the fall in arterial pressure and total peripheral resistance and the increased cardiac output was a significant increase in effective renal plasma flow ($p < 0.005$) and renal blood flow ($p < 0.001$) and

:mulating collagen disease caused by hydralazine (A
resoline) J.A.M.A 154 6 0 1954

'omens, P and Schroeder H A The L. E cell as a
manifestation of delayed hydralazine intoxication
.A.M.A 160 1134 1956.

)ammin G J Nora J R and Reardan J B Hydral
'zine reaction Case with L. E cells antemortem and
postmortem and pulmonary renal, splenic and muscular
esions of disseminated lupus erythematosus, J Lab
lin Med 46 806 1955

rohlich E D Kozul V., Tarazi, R L and Dustan
H P Physiological comparison of labile and essential
hypertension Circ Res. 26 (Supp 1) 55 1970

>eldinger S I Catheter replacement of the needle in
percutaneous arteriography Acta Radiol. Scand 15 368
1960

Smith, H W Finklestein N Aliminosa L. Crawford B.,
and Graber M The renal clearances of substituted
hippuric acid derivatives and other aromatic acids in the
dog and man J Clin Invest 24 388 1945

Anderson C F Sawyer T K and Cutler R E
Iothalamate sodium I vs. cyanocobalamin Co as a
measure of glomerular filtration rate in man J.A.M.A
204 105 1968.

Frohlich, E. D Clinical physiological classification of
hypertensive heart disease in essential hypertension in
Onesti, G Kim K. E., and Moyer H H., editors
Hypertension Mechanisms and management New
York, 19 3 Grune & Stratton Inc p 333

17 Chrysant S G and Lavender A R Direct renal
hemodynamic effects of two vasodilators Diazoxide and
acetylcholine Arch Int Pharmacodyn Ther 217 44
19 5

18. Velasco M., Gilbert C A., Rutledge C E and McNay
J L. Comparative cardiovascular effects of hydralazine
and a new antihypertensive agent bupicomide Circula
tion (abst.) 50 105 19 4

19 Gottlieb T B Katz, F H and Chidsey C A
Combined therapy with vasodilator drugs and beta
adrenergic blockade in hypertension A comparative
study of minoxidil and hydralazine Circulation 45 571
1972.

20. Gilmore E Weil J and Chidsey C A Treatment of
essential hypertension with a new vasodilator in combi
nation with beta adrenergic blockade N Engl. J Med
282 521 1970

21 Weil J V and Chidsey C A Plasma volume expansion
resulting from interference with adrenergic function in
normal man Circulation 37 54 1968

22 Dustan H P., Tarazi R. C., and Bravo E L.
Dependence of arterial pressure on intravascular volume
in treated hypertensive patients, N Engl J Med 286
861 19 2.

23. Ronnov-Jessen, V., and Hansen J Blood volume and
exchangeable sodium during treatment of hypertension
with guanethidine and hydrochlorothiazide Acta Med.
Scand 186 255 1969

Table IV Arterial pressure clinical and laboratory effects of bupicomide*

	Before		After		p<
Arterial pressure (mm Hg) (indirect recording)					
Supine					
Systolic	163	(4 6)	146	(6 4)	0 001
Diastolic	109	(3 4)	92	(3 4)	0 001
Standing					
Systolic	159	(5)	141	(6 1)	0 001
Diastolic	117	(4 2)	96	(4 3)	0 001
BUN (mg /100 ml)	13	(1)	14	(1)	N S
SGOT (Karmen units)	32	(2 8)	28	(2 7)	0 05
Alkaline phosphatase (U)	73	(7 2)	69	(6 2)	N S
Serum albumin (Gm/100 ml)	4 6	(0 1)	4 4	(0 1)	0 01
Total bilirubin (mg /100 ml)	0 6	(0 06)	0 6	(0 04)	N S
Hemoglobin (Gm /100 ml)	14 7	(0 5)	14 0	(0 5)	0 01
Hematocrit (vol %)	44	(1 1)	43	(3 9)	0 005

Each item represents the mean ± 1 S E M

effect was most likely restricted to arterioles and not to venules was shown by the lack of greater venous pooling during upright tilt and the marked increase in output in the supine position during therapy These inferences are supported further by the findings of significant reductions in mean arterial pressure and total peripheral resistance in the supine position associated with reflexive increase in heart rate cardiac output and left ventricular ejection rate

The systemic arteriolar dilatation and increased cardiac output was shared by the kidney as it was demonstrated by the significant increase in renal blood flow and decrease in renal vascular resistance Bupicomide had no effect upon the glomerular filtration rate reflecting significant vasodilation of both afferent and efferent arterioles and more so of the efferent arteriole which led to a significant decrease of the filtration fraction (Table III) Similar renal hemodynamic effects have been reported and with other vasodilators [6, 17] The systemic and renal hemodynamic changes produced by bupicomide were similar to those reported by Velasco and associates [18] These data suggest that bupicomide is a vasodilating agent with an action similar to hydralazine [1, 3, 7] Bupicomide therefore should be of value in the treatment of patients with essential hypertension, provided the compound is used in conjunction with agents that inhibit the reflex cardiac effects, such as the sympatholytics or beta adrenergic receptor inhibitors and also with diuretics to prevent expansion of intra volume with hypotension Such successful nations have been reported for hydralazine other vasodilators [19, 21] Bupicomide should a useful agent in the treatment of hyperte complicated with renal functional impairme

Summary

The systemic and renal hemodynamic eff bupicomide were studied in 10 male patients uncomplicated essential hypertension of mod ate severity Bupicomide significantly red systolic, diastolic, and mean arterial pressure peripheral vascular resistance and this hypo sive effect was associated with a reflexive incr in heart rate, left ventricular ejection rate cardiac index, it had no effect upon ot reflexive sympathetic adjustments induced upright tilt and the Valsalva maneuver B comide also increased renal blood flow decreased renal vascular resistance, but it had effect upon the glomerular filtration rate Th hypotensive mechanism of bupicomide there is mediated by peripheral arteriolar dilat through vascular smooth muscle relaxation T more immediate clinical side effects of b comide are related to its strong vasodila action and include headaches cutaneous ing and tachycardia

REFERENCES

1 Gross F Druey J and Meier R Eine neue Gru blutdrucksenkender Substazen von besonderem Wi kungs Karakter Experientia 6 19 1950

2 Tripod J and Meier R Détermination et classifica pharmacodynamigne de l action vasculaire périphér de l Apresoline du Nepresol et du Serpasil Arch I Pharmacodyn Ther 99 104 1954

3 Bein H J Gross F Tripod J and Meier R Exper mentelle Untersuchungen über die Kreislaufwirkung de blutdrucksenkender Hydralazinopthabazinderiva Apresolin und Nepresol Schweiz Med Wochens 83 336 1953

4 Schroeder H A Effects on hypertension of sulfhydr and hydrazine compounds J Clin Invest 30 6 1951

5 Schroeder H A The effect of 1 hydrazinophthala in hypertension Circulation 5 28 1952

6 Reubi F D Renal hyperemia induced in man by a ne phthlalazine derivative Proc Soc Exp Biol Med 73 102 1950

7 Wilkinson E L Blackman H and Hecht H H Cardiovascular and renal adjustments to a new hypoten sive agent (CIBA 5968) J Clin Invest 31 8 1952

8 Dustan H P Taylor R D Corcoran A C and Pa I A Rheumatic and febrile syndrome during pro hydralazine treatment J A M A 154 23 1954

9 Perry H M Jr and Schroeder H A Syndrome

and materials

al time clinical observation of cross sections ırdiac structures was attempted in 230 cases ı a Sonolayergraph (Toshiba Model SSL Fig 1) having a logarithmic amplifier ad of the standard equipped linear one In ı present sector scanning system a flat or ım focus transducer made of lead zircon titanate measuring 10 mm in diameter with .sonant frequency of 3 MHz was used at a tition rate of 3 6 KHz The transducer was hanically oscillated at the rate of 15 or 18 les a second that is to say at 30 or 36 cross tions per second by a scanner of which the ıng part was controlled to rotate alternately kwise and counterclockwise (Fig 2) The ıular position of the oscillating transducer was ected by a potentiometer The electric signals m the angular detector and those of rebound echoes from the transducer were transmitted oscilloscopes and the latter were displayed on m as B mode so that the angle of an individual ınning line equalled that of the transducer at e same instant (Fig 3) The oscillating angle of e transducer was arbitrarily opened to the aximum 90 degrees but the unblanking angle of e oscilloscope was fixed at about 65 degrees ıus although one image was theoretically mposed of 120 or 100 scanning lines (since the neration rate of the image was 30 or 36 per cond and the repetition rate of the pulse was 3 6 Hz) the scanning lines beyond the unblanking were eliminated When the oscillating ngle of the transducer was 90 degrees and 30 ames were generated per second one image was composed of 86 scanning lines (Fig 4) When the scillating angle of the transducer was smaller than the unblanking line the image was omposed of 120 or 100 scanning lines The angle etween two scanning lines was changed by etting the oscillating angle of the transducer To nable identification of echo sources a certain scanning line was selected manually and B mode was switched to M mode to obtain the echocar diogram

Patients were examined in the supine position occasionally when they had dilatated enlarged hearts they were turned slightly on their left side For the acoustic coupling between transducer and the chest the so called proximity immersed method was employed As the coupling medium

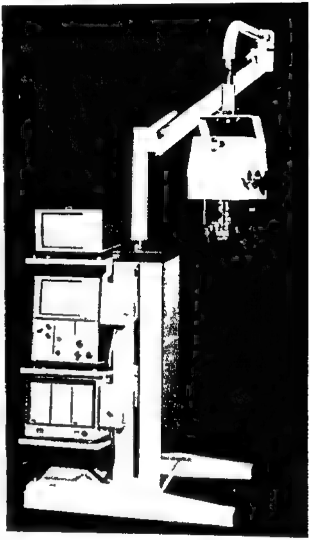

Fig 1 A full view of the Sonolayergraph (Model SSL-51H Toshiba)

castor or paraffin oil was used The transducer was immersed in the oil bag placed on the surface of the chest and was brought close to the same until multiple echoes from the bottom of the bag were eliminated The distance from the trans ducer to the chest surface was approximately 5 mm

A cross section along the left ventricular long axis was usually examined and for the determina tion of the plane the echoes of mitral leaflets and aortic root with valvular echoes within its lumen were detected as clearly as possible by manually operating the scanner After the setting of the cross-sectional plane the scanner was mechani cally operated at the rate of 30 cross sections a

Real-time observation of cardiac movement and structures in congenital and acquired heart diseases employing high-speed ultrasonocardiotomography

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Conventional echocardiography[1-6] is a useful method for examination of the heart since the echoes of the various cardiac structures are easily detected in a noninvasive way It is only one dimensional, however It would be valuable to have two dimensional direct information on anatomical relationships and to visualize cardiac structures At present, there are many techniques[7-14] available for this purpose and these technical approaches may be classified into two main groups one of them utilizes a multielement transducer and the other a single element The former method is called a multiscan, as introduced by Bom and associates[7] and King[8] The probe is composed of many transducer elements which are rapidly switched by electronics For each element, the detected signals of rebounding echoes are converted to dots and these are horizontally displayed on a cathode ray tube as a function of depth One image is made up of the
horizontal lines This method can
ly visualize two dimensional relationships
activities of the various cardiac structures
method of utilizing only a single transducer
first proposed by Ebina and co workers[9]
system consisted of a motor
a concave, focus transducer, and excellent
were produced at arbitrarily
the cardiac cycle In addition, King[10] utilized
compound contact scanner to obtain cross
sectional images synchronized with the QR
wave of the electrocardiogram (ECG) Th
images with his technique were also stati
Åsberg[11] obtained two dimensional informati
at the rate of seven frames a second by using
mirror system and cinematographic techniqu
Recently, McDicken and associates[12] achieved
frames a second by another method and Griffi
and Henry[13] introduced a new system to make
images per second Now, we[14] can obtain 30 or
images a second with a mechanical sector sca
ning system so as to observe heart
The possible application of this technique
clinical cardiac diagnosis is the purpose of th
paper

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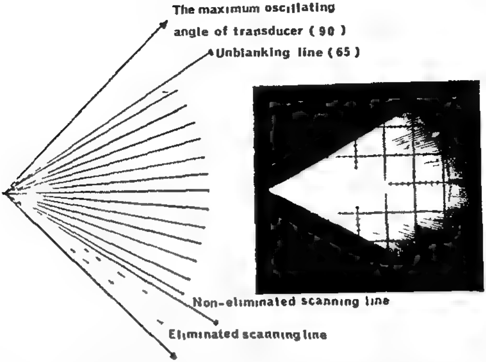


Fig 4 When the oscillating angle of the transducer is greater than the unblanking angle fixed at 65 degrees as shown at the left the scanning lines beyond the border are eliminated If the oscillating angle of the transducer is 90 degrees and the generation rate is 30 images per second one image is made up of 120 × 65/90 or 86 scanning lines as represented on the right. When the oscillating angle of the transducer is smaller than the unblanking angle no scanning lines are eliminated One image is made up of 120 or 100 scanning lines because of the repetition rate of 3 6 kHz and the generation rate of 30 or 36 images per second The angle between two scanning lines is changed with the set oscillating angle of the transducer

econd. At first the angle of sector scan was set at ull degree and thereafter it was opened grad ially to the maximum unless patients felt that he vibration transmitted from the oscillating ransducer was uncomfortable

Two methods were utilized to record the image on the oscilloscope screen First photographs were taken by a Polaroid camera or an ordinary 35 mm camera in synchronization with a QRS complex of the patient s ECG This allowed the recording of a single image at the selected moment in the cardiac cycle Occasional photo graphs were also taken at a shutter speed of 1/10 or 1/15 second without the triggering circuit The second approach was a cinematographic method with a commercially available 8 mm cinecamera The pulse generator of the camera was arranged to control the scanner and to produce 36 sector images a second In due consideration of a film feed time every other original image was recorded total of 230 patients were studied with the above system Several sample ultrasonocar diotomograms from the patients are presented in this paper

Results

The ultrasonocardiotomogram shown in Fig 5 was taken of a 31 year old subject in synchroniza tion with a QRS complex when a flat probe placed on the third intercostal space at a distance of 3 cm from the left sternal border scanned along the long axis of the left ventricle It is in systole corresponding to the CD interval on an echocardiogram of the anterior mitral leaflet This image was obtained by using a flat trans ducer and seems to have a laminal structure lateral resolution being insufficient to record the fine structures possible with the focus transducer (the lateral resolution will be discussed later)

In mitral stenosis some specific findings have been recognized by echocardiography Two dimensional echocardiograms in Fig 6 show

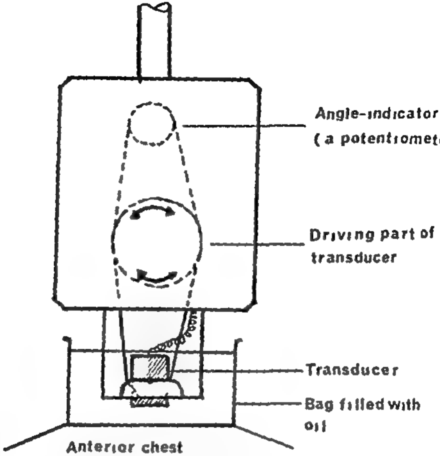


Fig 2 A diagram of the scanner The transducer is oscillated via a belt by the driving part which is controlled to rotate alternately clockwise and counterclockwise The angular position of the oscillating transducer is detected by a potentiometer For the acoustic coupling castor or paraffin oil is used

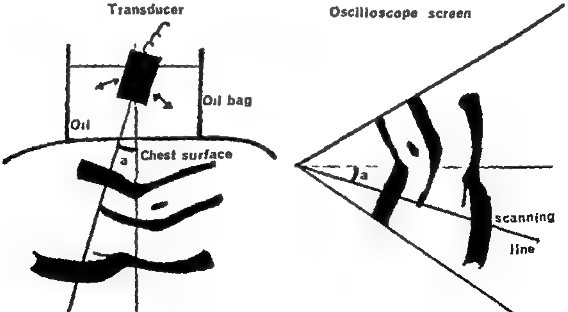
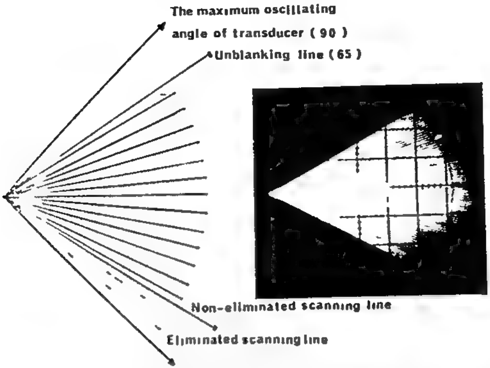


Fig 3 The relation between the angular position of the transducer and the corresponding scanning line on the oscilloscope screen The angle (a) of the individual scanning line on the screen is equal to that of the oscillating transducer at that instant on the left



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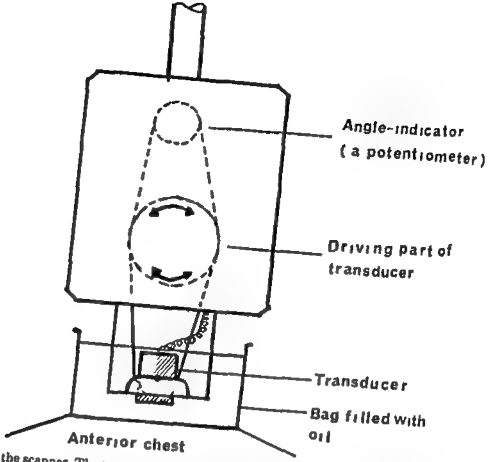

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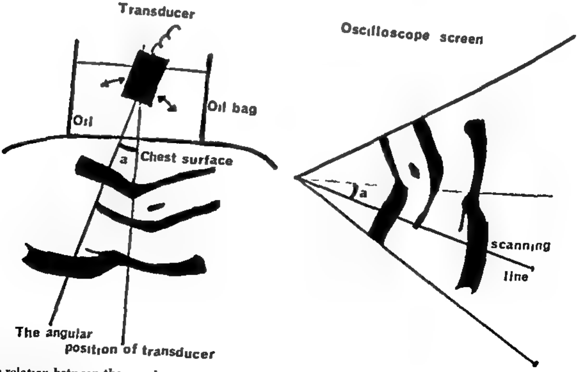

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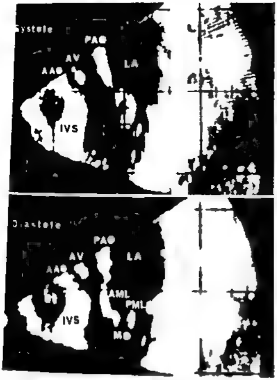


g 6 The tight mitral valve obtained by scanning the long is of the left ventricle in a 44-year-old woman with mitral enosis and aortic regurgitation The anterior mitral leaflet ulges into the outflow tract of the left ventricle at the eginning of diastole during which it remains ballooned gainst the left ventricle The movement of the leaflet tip is estricted and the orifice between both leaflets is narrower han that of a normal subject. At the onset of ventricular ontraction anterior mitral leaflet drifts toward the left itrium. *AV* = aortic valve *MO* = mitral orifice

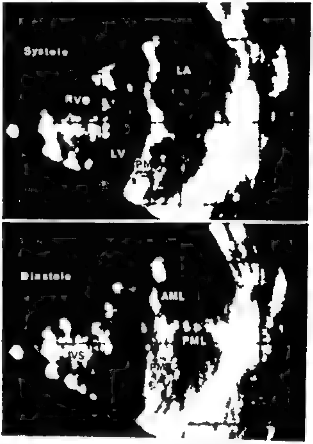


Fig 7 These frames showing a papillary muscle were obtained from a 35 year-old man with mitral stenosis. The upper is in systole and the lower in diastole The papillary muscle is more oblique in systole than in diastole and reflects mottled echoes. *PM* = papillary muscle

nformation on the volume overload of the right ventricle In addition to the paradoxical movement, the position of the interventricular septum may be a useful sign for the volume overload The frames in Fig 10 showing the positional change of the interventricular septum were obtained from the same patient as in Fig 9 Although the cross sectional plane is similar to that in which the long axis of the left ventricle is usually sectioned in normal subjects the left ventricle is somewhat obliquely cut The right ventricle is broad and the interventricular septum is inclined anteriorly as compared with those in Figs ▮ and 7 The positional change of the interventricular septum is probably caused by the dilatation of the right ventricle and the clockwise rotation of the heart.

As shown in Fig 11 the defect of the interventricular septum is directly visualized by two dimensional echocardiography The frames were made from a ▮ year old girl by scanning longitudinally along the left parasternal border The aortic wall and left ventricle are sectioned obliquely A discontinuity between the echo of the anterior aortic wall and the mottled echoes of the interventricular septum indicates a ventricular septal defect measuring about 15 mm in diameter

In contrast with the detection of an interventricular septum it is usually difficult to record an interatrial septum owing to the positional relationship The interatrial septum is located under the sternum which hinders ultrasonic beam penetration The picture in Fig 12 was taken of a 5 year old boy with a ventricular septal defect by scanning a plane rotated moderately counter clockwise to the horizontal from a long axis of the left ventricle Although an interventricular

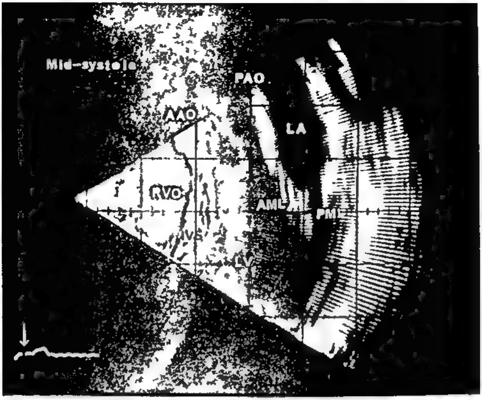


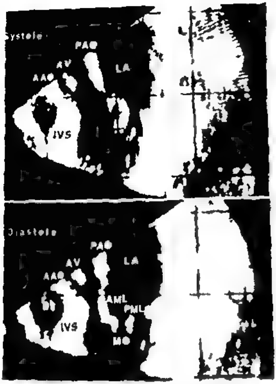
Fig 5 A cross section of left ventricular long axis taken in synchronization with the QRS complex with a flat transducer The white line in the lower left corner is an ECG the arrow indicates the moment in systole when the picture was taken The left ventricular posterior wall in the picture seems to have a laminal structure since a flat transducer was used *RVO* = right ventricular outflow tract *AAO* = anterior aortic wall *PAO* = posterior aortic wall *AML* = anterior mitral leaflet *PML* = posterior mitral leaflet *IVS* = interventricular septum *LV* = left ventricle *LA* = left atrium *ECG* = electrocardiogram

directly the narrowing mitral valve These pictures scanned along the long axis of the left ventricle were obtained from a 44 year old woman with mitral stenosis and aortic regurgitation, confirmed by cardiac catheterization and angiocardiography The upper picture is in systole and the lower in diastole In the latter the anterior mitral leaflet bulges into the outflow tract of the left ventricle The tip is posterior to the middle portion of the anterior mitral leaflet and its movement is restricted A mitral orifice between the anterior and posterior mitral leaflets is very narrow At the beginning of ventricular contraction, the anterior mitral leaflet drifts toward the left atrium and remains in contact with the posterior leaflet during the whole systole

The echoes of a papillary muscle were recorded occasionally Fig 7 shows a papillary muscle from another patient with mitral stenosis In systole the papillary muscle having mottled echoes is more oblique than in diastole Its top which cannot be clearly differentiated from that of chordae tendineae, moves posteroinferiorly with the anterior mitral leaflet and the base moves anteroinferiorly with the left ventricular posterior wall in systole

Although there are some difficulties in detecting aortic and pulmonic valves by two dimensional echocardiography owing mainly to their position clear two dimensional pictures of them were obtained as shown in Figs 8 and 9 Fig 8 shows the aortic valve of a patient with aortic regurgitation complicated by mitral stenosis which was diagnosed by cardiac catheterization and angiocardiography Two aortic cusps reflect strong echoes and the orifice between them (arrow) is smaller than that of the normal subject The anterior mitral leaflet also has a very strong echo and its movement is diminished Fig 9 shows a pulmonic valve cusp obtained from a patient with atrial septal defect These pictures were taken by scanning along the third intercostal space as the transducer was angled slightly upward from the horizontal The upper picture is in systole and the lower one in diastole The cusp which is probably a left one is cut in half in diastole In the upper systolic picture the cusp cannot be observed any longer

The interventricular septum provides useful



6 The tight mitral valve obtained by scanning the long is of the left ventricle in a 44 year-old woman with mitral enosis and aortic regurgitation The anterior mitral leaflet Iges into the outflow tract of the left ventricle at the ginning of diastole during which it remains ballooned gainst the left ventricle The movement of the leaflet tip is stricted and the orifice between both leaflets is narrower han that of a normal subject At the onset of ventricular ontraction, *anterior mitral leaflet drifts toward the left trium. AV* = aortic valve *MO* = mitral orifice

Fig 7 These frames showing a papillary muscle were obtained *from a 35 year-old man with mitral stenosis. The upper is in* systole and the lower in diastole The papillary muscle is more oblique in systole than in diastole and reflects mottled echoes. *PM* = papillary muscle

information on the volume overload of the right ventricle In addition to the paradoxical movement, the position of the interventricular septum may be a useful sign for the volume overload The frames in Fig 10 showing the positional change of the interventricular septum were obtained from the same patient as in Fig *9 Although the cross* sectional plane is similar to that in which the long axis of the left ventricle is usually sectioned in normal subjects the left ventricle is somewhat obliquely cut The right ventricle is broad and the interventricular septum is inclined anteriorly as compared with those in Figs 6 and 7 The positional change of the *interventricular septum is* probably caused by the dilatation of the right ventricle and the clockwise rotation of the heart.

As shown in Fig 11 the defect of the interventricular septum is directly visualized by two dimensional echocardiography The frames were made from a 5 year old girl by scanning longitudinally along the left parasternal border The aortic wall and left ventricle are sectioned obliquely A discontinuity between the echo of the anterior aortic wall and the mottled echoes of the *interventricular septum indicates a ventricular* septal defect measuring about 15 mm in diameter

In contrast with the detection of an interventricular septum it is usually difficult to record an interatrial septum owing to the positional relationship The interatrial septum is located under the sternum which hinders ultrasonic beam penetration The picture in Fig 12 was taken of a 5 *year old boy with a ventricular septal defect* by scanning a plane rotated moderately counterclockwise to the horizontal from a long axis of the left ventricle Although an interventricular

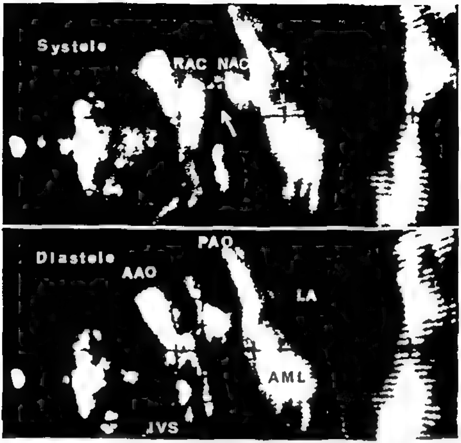


Fig 8 Two frames of two aortic cusps in a 44 year old man having an aortic insufficiency with mitral stenosis. There are strong echoes in both and an aortic orifice (arrow) is narrower than that of a normal subject. The movement of the anterior mitral leaflet having a strong echo is diminished The upper frame is in systole and the lower in diastole *RAC* = right coronary aortic cusp *NAC* = non-coronary aortic cusp

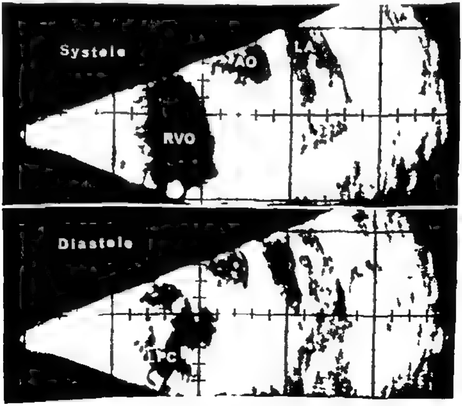


Fig 9 A pulmonic valve cusp of a 28 year old woman with atrial septal defect was observed when the approximately horizontal scanning was performed along the third intercostal space The upper picture is in systole and the lower in diastole In diastole the cusp probably the left one takes the form of a semicircle and faces the frontal plane *LPC* = left pulmonic valve cusp

Fig 10 A cross-section of the left ventricle scanned approximately along the long axis of the left ventricle in the same patient as in Fig 9 Interventricular septum is inclined anteriorly as compared with those in Figs 5 and 6 This may be due to the dilatation of the right ventricle and the clockwise rotation of the heart *LVPW* = left ventricular posterior wall

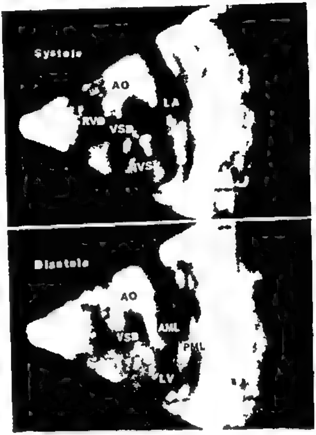


Fig 11 This cross-section was taken of a 5-year old girl with a ventricular septal defect by scanning longitudinally along the left parasternal line A discontinuity between the echoes of the anterior aortic wall and interventricular septum indicates a ventricular septal defect *VSD* = ventricular septal defect

septum was clearly recorded the defect of the septum could not be detected The interatrial septum and tricuspid leaflets are distinctly recognized The muscular interventricular septum leads to the interatrial septum via the membranous interventricular septum The anterior mitral leaflet and the septal tricuspid leaflet are in continuity with the interatrial septum The anterior tricuspid leaflet is opposite to the septal leaflet

Finally Fig 13 shows the rupture of a sinus of Valsalva into the right ventricle confirmed by operation These pictures were obtained by scanning a plane rotated slightly clockwise to the longitudinal from a long axis of the left ventricle as the transducer was angled medially The right coronary sinus is protruded and ruptures into the right ventricle (arrow) and the walls of the fistula reflect strong echoes The protrusion having the fistula moves inferiorly with the aortic wall in systole and comes back in diastole The aortic cusp seems to cover the sinus in systole

Discussion

Two dimensional information on the various cardiac structures is obtained with many available echocardiographic techniques [4] Among them the first mechanical scanning method was proposed by Ebina and associates[9] in 1967 Thereafter they [5] reported excellent frozen pictures in various diseases King[4] used a compound contact scan to make a stop action image of a section with a QRS trigger circuit With these methods however it is impossible to instantaneously observe heart movement Moreover it is difficult to use them with patients suffering from cardiac arrhythmia For close observation scanning speed must be fast enough to prevent flicker in images Asberg meanwhile succeeded in obtaining images at the rate of seven frames per

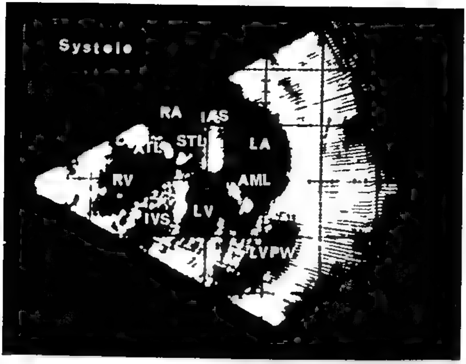


Fig 12 The systolic picture was taken of a 5 year old boy with ventricular septal defect by scanning a plane rotated moderately counterclockwise to the horizontal from a long axis of the left ventricle Interatrial septum and tricuspid leaflets are clearly recognized The muscular interventricular septum leads to the interatrial septum via the membraneous interventricular septum The anterior mitral leaflet and the septal tricuspid leaflet are in continuity with the atrial septum *RA* = right atrium *IAS* = interatrial septum *RV* = right ventricle *ATL* = anterior tricuspid leaflet *STL* = septal tricuspid leaflet

second with a mirror system in the same year as Ebina and associates introduced their scanning method Recently McDicken and associates[12] achieved 16 frames a second with another technique Griffith and Henry[13] described a system for obtaining real time images at 30 frames per second The method proposed by the present authors yields 30 or 36 images per second and allows real time observation of heart in action This technique is neither cumbersome nor time consuming A common feature of these methods is the use of a mechanical sector scan system

Multiscan echocardiography is similar to the mechanical type systems in the generation of real time images Since the multielement system—for example, Bom's—consists of an 8 cm array of 20 fixed ultrasound elements lateral resolution is not so good as the mechanical sector scanning systems Still, 160 images per second are produced and much more information on cardiac phases may be obtained It also allows a much greater area to be visualized near the chest wall because of its linear display For visualization of the right ventricle the multielement system therefore, is superior to mechanical sector systems, but the linear scan system, including multiscan, may be inferior to the sector scanning system for use with the various structures under the sternum and ribs With the mechanical sector scanning system the vibration the patient feels when the edges of the oscillating transducer contact the chest may be uncomfortable The multiscan system has no such uncomfortable vibration because the probe is not motor powered

Among mechanical type single element systems our system is similar to that of Griffith and Henry[13,14] and their associates in its generation rate of 30 images per second The most characteristic point of the present system is the wide oscillating angle of transducer and display angle on the oscilloscope screen The wide scanning and display are useful in practice since the wider the scanning and display angle, the more information is obtained in a single image Our image has 120 or 100 scanning lines a frame with display angle changeable from null to about 65 degrees, whereas Griffith s has 100 or 66 lines a frame with a fixed display angle of 45 or 30 degrees As a scanner the latter may be advantageous since a simple hand held scanner is utilized by direct contact method instead of the proximity immersed method But when the angle of oscillating transducer is much greater, the acoustic

oupling in the direct contact method may be incomplete since the wedge shaped gap between the transducer inclined at the maximum and the may not be promptly filled with a coupling . Moreover when the oscillating angle f transducer is greater the rocking vibration of the transducer in the direct contact method may ecome so strong that the patient feels some istress. This limitation was overcome with the proximity immersed method introduced by Tanaka and co workers[18]

As the ultrasound medium for echo sounding to and from the anterior chest, castor or paraffin oil s used in the present system instead of the conventional degasified water in the proximity mmersed method These oils act as insulators and shield the transducer Moreover they have a damping effect on ultrasound and diminish echo rebound off the walls of the oil bag or oil surface Furthermore the drive mechanism is enclosed to prevent any buildup on the moving parts. One possible pitfall however is that the wedge shaped oil layer between the transducer and the surface of the chest may distort the images since oils have lower acoustic impedances than the human body

With regard to the lateral resolution in this system it can be thought that the width of an ultrasound beam is about 10 mm at the distance of 75 mm from transducer surface when a 3 MHz transducer of 10 mm in diameter with flat face is used Therefore the lateral resolution is insufficient to record the fine structures and the image obtained seems to have a laminal structure (Fig 5) By using a 75 mm focus transducer having a narrower beam of which the width at the distance of 75 mm from transducer surface is about 5.5 mm better images are obtained (Figs 6 to 13)

Conventional echocardiography is a very useful noninvasive method for cardiac diagnosis and assessment For time analysis it is more convenient than two dimensional methods because the echocardiogram is a function of time which is easily measured at numerous points But since it is only one dimensional in depth it is difficult to directly visualize the anatomical relationships of various cardiac structures Moreover in the analysis of movements it may be theoretically impossible to record the movement of one fixed point by means of one dimensional method since by cardiac motion the point aimed at

Fig 13 The rupture of a sinus of Valsalva into right ventricle in a 45-year-old man. The right coronary sinus protrudes into the cavity of the right ventricle and the walls of the fistula reflect strong echoes. The protrusion indicated by an arrow moves with the aortic wall *AO* = aorta

initially may move out of the path of the ultrasonic beam while another point may move in at another moment of cardiac action The two dimensional method somewhat overcomes the limitation even through the movements in a cross-section are influenced by those across the plane

In clinical practice we can obtain much direct information on the various cardiac structures such as the four valves the papillary muscle the interventricular and interatrial septa and we can

observe the anatomical relationships in real time Moreover the abnormalities such as ventricular septal defect, stenotic mitral leaflets, and rupture of a sinus of Valsalva are more directly visualized in real time

Although some technical problems have still to be solved in this system it is considered to be especially useful as a fast, noninvasive method for cardiac diagnosis

Summary

Echocardiography has proved useful for cardiac diagnosis during the past several years, however, the conventional one dimensional ultra sound pulse echo method cannot easily visualize the anatomical relationships of the various cardiac structures To overcome the limitation the authors attempted a real time observation of cardiac structures and introduced high speed ultrasonocardiotomography with a Sonolayer graph Model SSL 51H (Toshiba) having a logarithmic amplifier

Thirty sector images are produced per second by a mechanically operated single flat or 75 mm focus transducer measuring 10 mm in diameter The angle of a sector image composed of about 120 scanning lines is arbitrarily changeable from null to 65 degrees The fast succession of images produced enables clear observation of the movement of cardiac structures in real time

Study of 230 patients by means of the proposed system suggests that it is advantageous as a quick method to provide two dimensional echocardiograms for cardiac diagnosis and assessment especially in noninvasive diagnosis

REFERENCES

1 Edler I and Hertz C H Ultrasound cardiogram in mitral valve disease Acta Chir Scand 111 230 1957
2 Feigenbaum H Echocardiography Philadelphia, 197 Lea & Febiger Publishers.
3 Popp R L and Harrison D C Echocardiography in Weissler A M editor Noninvasive cardiology New York and London 1974 Grune & Stratton Inc p 14
4 Ross F G M Ultrasonic investigation of heart, in Wells P N T editor Ultrasonics in clinical diagnosis Edinburgh and London 1972 Churchill Livingstone p 120
5 Feigenbaum H Clinical applications of echocardiography Prog Cardiovasc Dis 14 531 1972
6 Joyner C R editor Ultrasound in the diagnosis of cardiovascular pulmonary disease Chicago 1974 Year Book Medical Publishers Inc.
7 Bom N Lancée C T Zwieten G Kloster F E and Roelandt J Multiscan echocardiography I. Technical description Circulation 48 1066 1973
8 King D L Real time cross sectional ultrasonic imaging of the heart using a linear array multi element transducer J Clin Ultrasound 1 196 1973
9 Ebina T Oka S Tanaka M Kosaka S Terasawa Y Unno K Kikuchi Y and Uchida R The ultrasonotomography for the heart and great vessels in living human subjects by means of the ultrasonic reflection technique Jap Heart J 8 331 1967
10 King D L Cardiac ultrasonography Circulation 47 843 1973
11 Åsberg A Ultrasonic cinematography of the living heart Ultrasonics 6 113 1967
12 McDicken W N Bruff K and Paton J An ultrasonic instrument for rapid B scanning of the heart Ultrasonics 12 269 1974
13 Griffith J M and Henry W L A sector scanner for real time two-dimensional echocardiography Circulation 49 1147 1974
14 Takemura Y Nakagawa K Sato S Jingu M Nishimura K Hibi N Tada H and Kambe T High speed ultrasono cardiotomography by mechanical scanning Jap J Med Ultrasonics 1 24 1974
15 Tanaka M Neyazaki T Kosaka S Sugi H O'a S Ebina T Terasawa Y Unno K and Nitta K Ultrasonic evaluation of anatomical abnormalities of heart in congenital and acquired heart diseases, Br Heart J 33 686 1971
16 Henry W L Maron B J Griffith J M Redwood D R and Epstein S E Differential diagnosis of anomalies of the great arteries by real time two dimensional echocardiography Circulation 51 283 1975

ɔcalization by autoradiography of tritiated ɔoproterenol in "infarct-like" lesions of rat yocardium

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number of physiopathogenic mechanisms have een outlined to explain the infarct like lesions roduced by isoproterenol (ISP) in the hearts of arious animals. Since the first observation of happel and associates[1] in 1959 many papers ave been published on this subject[2-1] with vari tions in the dosage and species of animals sed.

Nevertheless the common denominator of the bservations made by optical microscopy 24 ours after intraperitoneal injection of isoprote enol include localized necrosis myocytolysis omogenization fibrillar degeneration and a ositive test for ischemia [8] (Fig 1)

The mechanisms that have been proposed to xplain these findings include excess of oxygen consumption and inotropic effect coronary vasoconstriction deleterious action on glucose and lipid metabolism [5] direct cardiotoxic ef fect, platelet aggregation in the small cardiac vessels and formation of microclots excessive mobilization of fatty acids [20] fluid and electrolytic alterations,[21] loss of high energy intracellular coupling [22] and inadequate activation of the cal cium pump [23]

For this reason localization of the tritiated ISP in the normal myocardial fibers and in the induced lesions was studied Tritium has a half life of 12 1 ± 0 5 years which is more than adequate for the design of this study

From the Di isi n f Pathol gy Hosp tal Fernand z, Buenos Aires, Republic Arge ti a.

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Materials and methods

The first group (G 1) was used as a control and consisted of 40 Wistar rats weighing from 180 to 200 grams ISP sulfate 10 mg per kilogram was injected intraperitoneally Under ether anesthe sia the rats were killed in groups of eight each 5 30 and 120 minutes and 12 and 24 hours after the injection A second group of 40 rats (G 2) was given the same dose of ISP which contained 5 μCi of tritium (^{3}H) in carbon 7 The animals of this group were killed at the same intervals

A complete autopsy was performed on all 80 animals The entire heart was sectioned trans versely in slices 1 mm thick.

The organs were fixed in formol calcium and 10 per cent neutral formalin Paraffin and frozen sections were obtained serially from the 1 mm slices.

The following staining materials were used hematoxilin-eosin Gomori and Barbeito-Lopez [5] trichromic stains the ischemia stain[12] (basic fuch sin hematoxilin and picric acid stain) fuchsin acid stain (Selye) [26] and stains for acid phospha tase[27] and succinic dehydrogenase [28] Electron microscopy was also used with conventional methods

Autoradiography was performed with a Kodak Grain autoradiographic stripping plate (A R 10) The tritiated isoproterenol (H) was supplied by the New England Laboratories (Boston) Ra dioautographs were obtained with the method previously described [29-1] The slides were made by covering the paraffin and frozen sections (10 μ thick) with cromic gelatin and then transferred to a water bath. They were dried covered with the stripping film and stored at −4° C for 15 to 21

Fig 1 Early positivity demonstrated by the ischemia test left ventricular subendocardium 5 minutes after the injection of isoproterenol sulfate 10 mg per kilogram Ischemia is shown by black (red) stain inside the fibers (Basic fuchsin hematoxilin and picric acid stain)

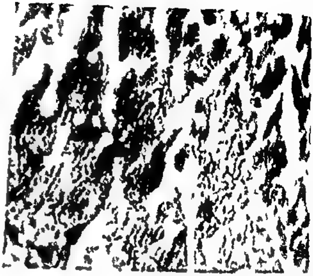

Fig 3 As shown in Fig 2, deposit of the labeled drug on the sarcolemma and smaller quantity inside the myocardial fibers—radioautography stripping film technique

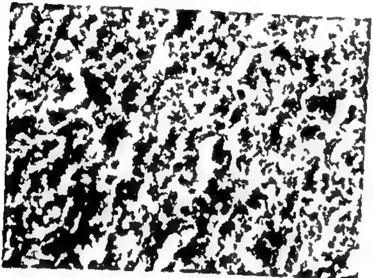

Fig 2 An abundant amount of labeled drug was observed on the sarcolemma surface and a smaller quantity was noted inside the myocardial fibers Animals killed 24 hours after the injection of ISP H 5 μCi—radioautography stripping film technique

Fig 4 In animals killed 5 and 30 minutes after injection, the deposit was noted in grooves along the edge of the sarcolemma suggesting a primary action on the cellular membrane—radioautography stripping film technique

days Silica gel granules were used to reduce humidity Special care was taken in the management of the material and the technique was finished in 10 minutes in the frozen sections

Development of the photographic film was carried out in accordance with the instructions packaged with it

Both the control and post treatment specimens were stained with toluidine blue (10 per cent) for 10 minutes To rule out pseudophotographic effects, specimens of the control group were subjected to the same procedure The serial sections were examined to localize the labeled drug and topographic distribution of the radioactivity was established

Results

Lesions similar to those described by others[11,12] were found in all animals of each group

Five minutes after the injection, myofibrils with contracture bands' and fibrillar disorganization were noted After 2 hours homogenization of the fibrils and microvacuolization were observed

The test for ischemia, described by Lie and associates[13] was positive and reduced levels of

...amidehydrogenase and acid phosphatase ...e observed in all specimens After 24 hours ...l infarct like lesions were totally established ...h mononucleocytes, zones of homogenization ...l myocytolysis.

...n rats treated with ISP ³H an abundant ... of labeled drug was observed on the ... and a smaller quantity was ...ted inside the myocardial fibers (Figs 2 and 3) ...is observation was noted in the autoradio...phs obtained 5 minutes after the injection and ...sisted at all subsequent observation times As shown in Fig 4 and particularly in those ...imals which were killed 5 and 30 minutes after ...ection the deposit was noted in grooves ...ong the edge of the sarcolemma strongly ... a primary action on the cellular ...embrane Comparison of the normal ischemic ...d necrotic areas and the localization of the ...beled drug revealed a correlation between the ...e of localization of the radioactivity and the ...cation of the myocardial necrosis No signifi...nt differences were observed between paraffin ...d frozen sections

...iscussion

In previous papers[23] attention has been called ...the fact that the catecholamine effect on the ...yocardium is mainly an action on the ... resulting in an increase in the activity ... the intracytoplasmic calcium pump The ... made in this study support the ... other authors who suggested a ...direct cardiotoxic effect

From our data, the deposit of the labeled drug ...in the sarcolemma surface suggests that the ...ial point in the ISP induced lesions is an ...abundant Ca influx a state of excitation contrac...tion overcoupling in which the myocardial ...fibers are killed if they cannot get rid of the Ca ...overload The assumption that the site of locali...zation of the radioactivity is the same as that where the effect leading to cardiac necrosis occurs should be discussed in view of the fact that isoproterenol is a soluble compound with signifi...cant loss of radioactivity during the processing of tissues but the careful and rapid handling of the processing and the deposit itself on the membrane give value to this observation

The possibility of diffusion artifact cannot be completely ruled out. One would think that partial losses of radioactivity would occur by different diffusion mechanisms although this does not reduce the importance of our observation However observations by previous investigators using different fixation techniques makes this possibility less likely [29]

This fundamental effect on the membrane has been described by others investigators. In 1964 Rosenmann and associates[7] described ISP induced lesions in rat myocardium similar to those produced by potassium deficiencies with a clear change in the membrane potentials These observations were corroborated by Selye[33, 34] Follis and associates,[37] and Schrader and associates.[38]

Hypercontraction of occasional cells[39] was demonstrated by electron microscopy within 2 minutes of the intraperitoneal injection of ISP By 8 minutes, muscle cells showed contraction bands and foci of mitochondrial calcification This sequence suggests early cell damage and release of calcium from the sarcoplasmic reticulum Uptake of calcium by metabolically competent mitochondria is also suggested[41] Calcium deposition occurs when the ATP generation ceases but the mitochondria are still capable of respiration Janke and associates[11] demonstrated the relevance of the calcium pump in the excitation contraction coupling These authors also found inhibition of lesions caused by ISP by the action of compound D600 (Knoll) as measured by the lowering of the calcium content in rat hearts.[40, 41] Further they found an increase of ⁴⁵Ca uptake in the ventricles of rats produced by ISP Also reduction of Ca uptake was provoked by several agents capable of uncoupling the excitation contraction phenomenon

We recently noted[42] the inhibition by prenilamine lactate[43] of infarct like lesions caused by ISP in rats Prenilamine lactate decreases Ca transport through the endoplasmic reticulum [43]

These findings and the peculiar topography of tritiated drug suggest the following (1) Myocardial necrosis induced by ISP is probably due to an increased activation of the calcium pump This phenomenon leads to increased consumption of coupling high-energy bonds and cellular death The early presence of contracture bands and the positivity of the ischemia test further emphasize this statement (2) The ISP effect is rapid (3) The morphologic alterations described in this paper are similar to those described by Baroldi. He showed coagulation myocytolysis as present in

the human infarction or following sudden death Therefore, the heart lesions provoked by ISP appear to be a promising model for studying the pathological mechanisms involved in human myocardial infarction

Summary

A number of physiopathogenic mechanisms have been outlined to explain the infarct like' lesions produced by isoproterenol (ISP) in the hearts of various animals Excess of oxygen consumption and inotropic effect coronary vaso constriction, deleterious action on glucose and lipid metabolism, direct cardiotoxic effect, plate let aggregation in the small cardiac vessels and formation of microclots excessive mobilization of fatty acids, fluid and electrolytic imbalances, loss of high energy intracellular coupling, and in adequate activation of the calcium pump

For this reason localization of the tritiated ISP in the normal myocardial fibers and in the induced lesions was studied

The first control group (G 1) consisted of 40 Wistar rats, weighing from 180 to 200 grams, they were injected intraperitoneally with ISP sulfate (10 mg per kilogram) and were killed under ether anesthesia after periods of 5 30 and 120 minutes, and 12 and 24 hours

A similar group (G 2) was injected intraperi toneally with an equal dose of ISP plus 5 μCi of tritiated ISP sulfate (^3H) In this group animals were killed at the same periods as above

In rats treated with ISP ^3H an abundant amount of the labeled drug was observed on the sarcolemma surface and a smaller quantity was noted inside the myocardial fibers This observa tion was noted in the autoradiographs obtained 5 minutes after the injection and persisted in all subsequent observation times In those animals which were killed 5 and 30 minutes after injec tion, the deposit was noted in ' grooves ' along the edge of the sarcolemma strongly suggesting a primary action on the cellular membrane

These findings and the peculiar topography suggest that (1) myocardial necrosis induced by ISP is probably due to an increased activation of the "calcium pump , the early presence of contracture bands and the positivity of the ischemia test further emphasize this statement, (2) the ISP effect is rapid, (3) the morphologic alterations are similar to those recently described as coagulation myocytolysis and present in human infarctions or following sudden death.

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REFERENCES

1 Chappel C I Rona G Balazs T and Gaudry R Comparison of cardiotoxic actions of certain sympathomimetic amines, Can J Biochem Physiol 37 [illegible] 1959
2. Rona [illegible] Zsoster T Chappel C and Gaudry R. Myocardial lesions, circulatory and electrocardiographic changes produced by isoproterenol in the dog Rev Can Biol 18 [illegible] 1959
3 Rona G Chappel C I Balazs T and Gaudry R. [illegible] infarct like myocardial lesion and other toxic manifestations produced by isoproterenol in the rat, Arch. Pathol 67 443 1959
4 Handforth C P Myocardial infarction in hamsters produced by isoproterenol Med Serv J Can 18 [illegible] 1962
5 Handforth C P Isoproterenol induced myocardial infarction in animals Arch Pathol 73 161 1962
6 Wexler B C and Kittinger C W Myocardial necrosis in rats Serum enzymes adrenal steroid and histopathological alterations, Circ Res 13 159 1963
7 Rosenmann F Gazenfield L Laufer A and Davies A M Isoproterenol induced myocardial lesions in the immunized and nonimmunized rat Pathol Microbiol 27 303 1964
8 Chappel I C Rona G Balazs T and Gaudry R. Severe myocardial necrosis produced by isoproterenol in the rat Arch Int Pharmacodyn Ther 122 123, 1959
9 Zbinden G and Bagdon R E Isoproterenol induced heart necrosis an experimental model for the study of angine pectoris and myocardial infarct Progress in muscle research Part II Cardiac muscle Rev Can F L Symp 257 1963
10 Rona G and Chappel I C The effect of breed age and sex on myocardial lesions and other toxic manifestations produced by isoproterenol in the rat Arch Pathol 67 443 1959
11 Wexler B C and Judd J T Acute myocardial histopathology in normal and arteriosclerotic rats during isoproterenol induced infarction Br J Exp Pathol 51 646 1970
12 Lie J T Holleg K E Kampa W [illegible] and Titus, J L New histochemical method for morphologic diagnosis of early stages of myocardial ischemia Mayo Clin Proc 46 319 1971
13 Schenk E A and Moss A J Cardiovascular effects of sustained norepinephrine infusions II Morphology Circ Res 18 605 1966
14 Maling H M and Highman B Exaggerated ventricular arrhythmias and myocardial fatty changes after large doses of norepinephrine and epinephrine in unanesthetized dogs Am J Physiol 194 590 1959
15 Nahas G C Brunson J G King W M and Cavert H M Functional and morphologic changes in heart lung preparations following administration of adrenal hormones, Am J Pathol 34 717 1958
[illegible] Fleisher M S and Loeb L Experimental myocarditis Arch Intern Med 3 78 1909
17 Szakacs J E and Cannon A / Norepinephrine myocarditis, Am J Clin Pathol 30 425 1958

Haft, J I Kranz, P D., Albert, F L., and Fani, K Intravascular platelet aggregation in the heart induced by norepinephrine Circulation 46 698 1972.

Haft, J I and Fani, K. Stress and the induction of intravascular platelet aggregation in the heart Circulation 48 164 1974.

Rona G Kahn, D S., and Chappel C I Studies on infarct like myocardial necrosis produced by isoproterenol A review Rev Can. Biol. 22 241 1963

Rona, G Kahn D S and Chappel, C I The effect of electrolytes on experimental infarct like myocardial necrosis, in Bajusz, E., editor Electrolytes and cardiovascular disease Basel/New York, 1965 S Karger AG p. 181

Janke, J Jaedicke, W and Fleckenstein A. Prevention of isoproterenol induced cardiac necrosis by reduction of transmembrane Ca influx with the use of K and Mg salts or of Ca antagonists inhibitors of excitation-contraction coupling, Pflügers Arch. Ges. Physiol R8 319 1970

Janke J Fleckenstein A and Jaedicke W Inhibition of the isoproterenol induced radiocalcium uptake into the ventricular myocardium by Ca antagonistic inhibitors of excitation-contraction coupling (Isoptin verapamil, iproveratril or compound D600 Pflügers Arch. Ges. Physiol. R10 316, 1970

Fitzgerald, M. L., Eidinoff M L., Knoll, J E. Simmel, E. B. Tritium in radioautography Science 114 494 1951

Barbeito-Lopez, L A new trichome stain Am. J Clin Pathol Tech. 16 53 1946

Poley R. W and Fobes, C D Fuchsinophilia in early myocardial infarction Arch. Pathol. 77 317 1964

Pearse, A. G Histochemistry Edinburgh and London 1972, Churchill Livingstone.

Burstone, M. S Modifications of histochemical techniques for the demonstration of cytochrome oxidase J Histochem. Cytochem. 9 59 1961

Appleton, T C *In Roth, L. I and Stumpf W E.,* editors Autoradiography of diffusible substances, New York, 1969 Academic Press, Inc pp 301 319

Dawson K. B Differential autoradiography of tritium and another emitter by a double stripping film technique Nature 195 510 1962.

Joftes, D L. Simplified liquid emulsion radioautography J Biol. Photogr Assoc 23 145 1955

32. Kodak Materials for Nuclear Physics and Autoradiography Eastman Kodak Company N Y

33. Maruffo, C Fine structural study of myocardial changes induced by isoproterenol in rhesus monkeys (*Macaca mulatta*) Am. J Pathol. 50 27 1967

34. Wexler B C Judd, J T., and Kittinger G W Myocardial necrosis induced by isoproterenol in rats. Changes in serum protein, lipoprotein, lipids and glucose during *active necrosis and repair in arteriosclerotic and non* arteriosclerotic animals, Angiology 19 665 1968.

35. Selye, H Chemical prevention of cardiac necrosis, New York, 1959 Ronald Press.

36. Selye, H. The pluricausal cardiopathies, Springfield, Ill., 1961 Charles C Thomas, Publisher

37. Follis, R. H., Orent-Keilese, E., and McCallum, E. V Production of cardiac and renal lesions in rats by a diet extremely deficient in potassium, Am. J Pathol. 18 29 1942.

38. Schrader G A., Prickett, C O and Salmon W D Symptomatology and pathology of potassium and magnesium deficiencies in the rat, J Nutr 14 85 1937

39. Bloom, S., and Cancilla, L Myocytolysis and mitochondrial calcification in rat myocardium after low doses of isoproterenol, Am. J Pathol. 54 373, 1969

40. Fleckenstein, A. Myokardstoffwechsel und Nekrose Heilmeyer L., and Holtmeier H. J., editors VI Symposium der Deutsch. Ges. für Fortschritte auf dem Gebiet. der Inneren Medizin über "Herzinfarkt und Schook," Freiburg, November 1968, Stuttgart, 1968 Georg Thieme Verlag, p 94

41. Fleckenstein, A., Döring, H. J., Grün G and Kammermeier H *Influence of Prenylamine on the utilization of* high energy phosphates in cardiac muscle—Biochemical aspect of Prenylamine, Biochim. Appl. 1 (Suppl.) 323, 1968.

42. Miles, J., and Rapaport, M. Inhibition by prenylamine of the lesions produced by isoproterenol in the myocardium of rats. VII World Congress of Cardiology Buenos Aires, 1974

43. Naylor W G Biochemical aspects of prenylamine action preliminary communication. Biochemical aspects of prenylamine Biochim. Appl. 14 (Suppl.) 305 1968

44. Baroldi, G Pathologic changes in coronary heart disease. An over view on their significance. Cardiologisches Bulletin, Acta Cardiol. 8/9 133 1974.

Conduction disturbances of the bundle branches produced by lesions in the nonbranching portion of His bundle

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It is believed that conduction disturbances of the bundle branches are due to lesions in the corresponding bundle branches[1-3], however evidence is also available to suggest a possible participation of the His bundle in the development of bundle branch block James and Sherf[4] demonstrated that the His bundle of canine or human hearts is composed of bundles of Purkinje type fibers which are longitudinally oriented and separated by the connective tissue These bundles were shown to be joined by transverse crossover connections at various intervals along their longitudinal axes Accordingly, they postulated the possibility that various forms of aberrant ventricular conduction could result from an impulse traversing the His bundle with a nonuniform front of activation Because of its nonuniformity the impulse would reach the various bundle branches at unequal times producing a significant alteration in the sequence of ventricular activation or a pattern of bundle branch block

The above theory implies that the His bundle and bundle branches have a longitudinal core wire" organization of their fibers which would favor predestination of impulse transmission at the level of His bundle If this hypothesis is correct, a lesion in the His bundle would result in an interruption of impulse propagation to the corresponding bundle branches and aberra ventricular conduction The present study w conducted to demonstrate that localized lesi in the nonbranching portion of His bundle co indeed produce the bundle branch block und certain conditions

Methods

Hearts were excised from mongrel dogs anes thetized with sodium pentobarbital (30 mg. pe kilogram intravenously) The portion of the hea consisting of a part of the atrial septum, corona sinus the base of the aorta and the upper port of the interventricular septum was rapidly dissected and placed in a tissue bath with conti uous infusion of the oxygenated Tyrode solu A slightly modified technique of dissection of the A V node, His bundle, and bundle branches a described by Tse[5] and Elizari and associates[6] wa used In order to facilitate the simultaneo impalement of microelectrodes in the righ bundle branch and the anterior and posteri divisions of left bundle branch, the followi arrangement of the preparation was made On the preparation was trimmed to its final dime sion the interventricular septum was slit alo the axis of the A V node and His bundle t incision was stopped at about 3 to 4 mm from t His bundle The removal of the atrial and conne tive tissues overlying the A V node His bund and bundle branches was done carefully wit sharp scalpel blade and a pair of ophthalm scissors under a dissecting microscope T conduction tissues, once exposed, appeared pa and readily identifiable from the darker nei boring septal myocardial tissues The s septum was then spread and pinned to a para

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of a tissue chamber which served as a
orm with all the conducting tissues exposed
horizontal plane The preparation was then
ed to rest for 2 hours

1 shows a line drawing of such a prepara *Area 1* is the A V node and *areas 2 3* and *4* the upper middle and lower portions of branching His bundle (HB) The middle on of HB (*area 3*) was the site in which a n was made in all experiments The upper (*area 2*) was the site of pacing for all control rvations and also was proximal to the site of lesion The lower HB (*area 4*) was the site of ng distal to the lesion *Areas 5 6* and *7* are posterior and anterior divisions of left bundle ich (LPD and LAD) and the right bundle ich (RB) respectively A pair of bipolar inum wire stimulating electrodes was used to e the preparation at either the upper or lower tion of the HB A series of Tektronix wave n and pulse generators were used to deliver ing stimuli to the stimulating electrodes The paration was paced by applying suprathresh (2 × threshold) rectangular pulses of 2 msec ation at various basic cycle lengths (BCL) e reason for pacing the upper HB instead of the V node was that the A V node often failed to spond 1 1 to rapid pacing stimuli during the ntrol observation under the present experi ntal conditions

Modified Tyrode s solution equilibrated in a ervoir with 95 per cent O_2–5 per cent CO_2 was ed to superfuse the preparations The tempera re of the bath was maintained between 37 and C The millimolar composition of the Tyrode s solution was NaCl 137 dextrose 5 5 KCl 17 CaCl 2 7 $MgCl_2$ 0 5 $NaHPO_4$ 12 5 Glass microelectrodes filled with 2 7M KCl were used to cord transmembrane action potentials The sistance of these electrodes ranged from 20 to 30 megohms A silver wire indifferent electrode was n contact with the Tyrode s solution in the bath n all experiments three microelectrodes were used to record action potentials from fibers of the LPD LAD and RB simultaneously at 5 to 10 mm from the lower portion of the nonbranching HB The impulses initiated at the HB and conducted to the LPD LAD and RB were monitored by these three strategically positioned roelectrodes These action potentials were displayed on an oscilloscope and photographed with a Grass camera

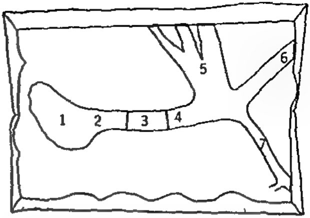

Fig 1 Drawing of the preparation of exposed His bundle and bundle branches *Area 1* = the A V node *2 3* and *4* = the upper middle and lower portions of nonbranching His bundle (HB) 5 and 6 = the posterior and anterior divisions of left bundle branch (LPD and LAD) 7 = the right bundle branch (RB) A left or right sided lesion was made by 50 per cent transection of the HB in *area 3* See text for more details.

Results

When the upper portion of HB was paced at a short BCL (160 to 320 msec) before a lesion was made in the HB impulses were conducted in a 1 1 relationship to the three recording sites in the LPD LAD and RB A lesion was then made in the middle portion of HB on either the left or right side by transection of about 50 per cent of the cross sectional area Following such a cut a moderate increase in the spontaneous activity occurred in many preparations which generally returned to the previous level in about 15 minutes The preparation was again paced at the upper portion of HB proximal to the lesion at the same BCL to observe the development of conduc tion block to any of the recording sites in the bundle branches The BCL was then increased stepwise in order to obtain the shortest BCL at which 1 1 conduction to all three branches was restored In order to substantiate that block occurred at the site of lesion at a short BCL the pacing electrodes were carefully moved to the lower portion of HB distal to the lesion and the pacing was repeated at the same short BCL as before the lesion When this was done 1 1 conduction of all three branches could be estab lished.

Table I shows the results of eight experiments with the left sided lesion In three out of the eight experiments partial or complete block was observed only in the ipsilateral branch (LPD

Table I Experimental data of left sided lesions

Exp No	Pacing before lesion	Pacing proximal to lesion		Pacing distal to lesion
	Shortest BCL for 1 1 conduction to all branches (msec)	*Nature of block during pacing at short BCL*	*Shortest BCL for 1 1 conduction to all branches (msec)*	*Shortest BCL for 1 1 conduction to all branches (msec)*
1	200	Partial block to LPD LAD RB	630	200
2	250	Complete block to LPD LAD RB	No conduction	200
3	250	Partial block to LPD LAD	400	250
4	200	Partial block to LPD	500	200
5	250	Complete to LPD LAD RB	No conduction	250
6	250	Partial block to LPD LAD	400	250
7	160	Partial block to LPD LAD RB	630	160
8	200	Partial block to LPD LAD RB	500	200

Abbreviations BCL = basic cycle length LPD = the posterior division of left bundle branch LAD = the anterior division of left bundle branch RB = the right bundle branch

Table II Experimental data of right sided lesions

Exp No	Pacing before lesion	Pacing proximal to lesion		Pacing distal to lesion
	Shortest BCL for 1 1 conduction to all branches (msec)	*Nature of block during pacing at short BCL*	*Shortest BCL for 1 1 conduction to all branches (msec)*	*Shortest BCL for 1 1 conduction to all branches (msec)*
1	250	Partial block to RB	400	250
2	200	Partial block to LPD LAD RB	400	200
3	320	Partial block to RB	450	250
4	200	Complete block to RB	600	00
5	200	Partial block to LPD LAD RB	320	200
6	160	Partial block to RB	400	200
7	250	Partial block to LPD LAD RB	500	250
8	300	Complete block to LPD LAD RB	No conduction	300

Abbreviations same as in Table I

and/or LAD) at short BCLs In the remaining five preparations such conduction block occurred in the bilateral branches (LPD, LAD, and RB) at short BCLs Table II shows the results of another eight experiments with the right sided lesion Partial or complete block occurred in the ipsilateral branch (RB) in four experiments and in the bilateral branches (LPD LAD and RB) in the remaining four experiments during pacing at short BCLs These results also show that in nine out of all 16 experiments conduction block occurred in the bilateral bundle branches regardless of the side of the lesion In comparing the results of left and right sided lesions, the shortest BCL required to maintain 1 1 conduction to all three bundle branches was much longer in both groups after the lesion but the left sided lesion produced a greater increase in the shortest BCL for 1 1 conduction

Selective block to the LPD and LAD Fig 1 shows the results of one of the three experiments in which selective conduction block occurred in the left bundle after a left sided lesion was made. *Panel A* shows the control recording with the first second and third tracings being action potentials recorded from the LPD LAD, and RB, respectively The bottom tracing shows the pacing stimulus artifacts Impulses were initiated by pacing stimuli applied to the upper portion of HB at a BCL of 250 msec and these impulses were conducted to LPD LAD and RB in a 1 1 relationship *Panel B* shows the results of pacing the HB at a BCL of 300 msec after a left sided lesion was made The pattern of impulse conduction to the three branches changed considerably Impulses arriving at the microelectrode in the LPD showed a distinct partial block of a 2 1 ratio, whereas those arriving at the LAD show an

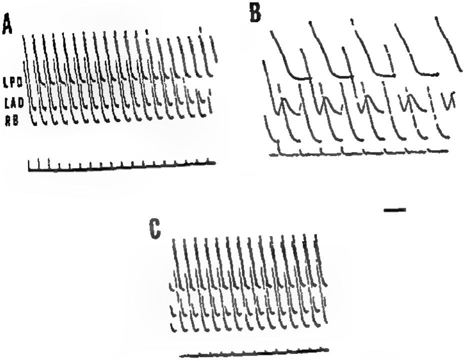

Fig 2 Partial block to the LPD and LAD after a left sided lesion *Panel A* = the control at BCL of 250 msec *B* = pacing proximal to the lesion at BCL of 400 msec *C* = pacing distal to the lesion at BCL of 250 msec Horizontal calibration line = 500 msec for *A* and *C* and 300 msec for *B*

ternative pattern of full action potentials and electrotonic local responses These were in contrast to those impulses arriving at the RB which showed full action potentials in a 1 1 ratio 1 1 conduction to all three branches could be observed only when the BCL was increased to 400 msec In *panel C* however when the stimulating electrode was carefully shifted to the lower HB distal to the lesion impulses were conducted to all three branches in a 1 1 ratio at the same BCL of 250 msec as in the control

Selective block to the RB Fig 3 shows the results of one of the four experiments in which selective block occurred in the RB after a right sided lesion was made *Panel A* shows the control recording from the LPD LAD and RB Impulses initiated by pacing of the HB at a BCL of 320 msec propagated to all three branches in a 1 1 ratio After a right sided lesion was made 1 1 conduction of impulses to the three branches could be obtained only when the BCL was increased to 450 msec *Panel B* shows that when the HB was paced at a BCL of 400 msec 2 1 block occurred in the RB while 1 1 conduction was still maintained to the LPD and LAD The interval between the stimulus artifact and the beginning of phase 0 depolarization increased in the RB This probably reflects slower conduction of impulses from the site of lesion to the microelectrode in the RB The slow conduction of impulses was probably due to an increase in the slope of phase-4 depolarization reflecting an increase in automaticity of the fiber as a result of less frequent excitation In other words the arrival of impulses at a less negative membrane potential resulted in slower conduction In *panel C* however impulses initiated by pacing of the HB distal the lesion at a BCL of 250 msec could again propagate to the three branches in a 1 1 relationship

Block to the bilateral bundles (LPD LAD and RB) The results of nine experiments indicated that either partial or complete block was manifested in all three bundle branches regardless of the side of the lesion Fig 4 shows the typical results of one of the six experiments in which partial block was observed in the bilateral bundles *Panel A* shows the control recording in which impulses were conducted to all three branches at a BCL of 250 msec In *panel B* after a

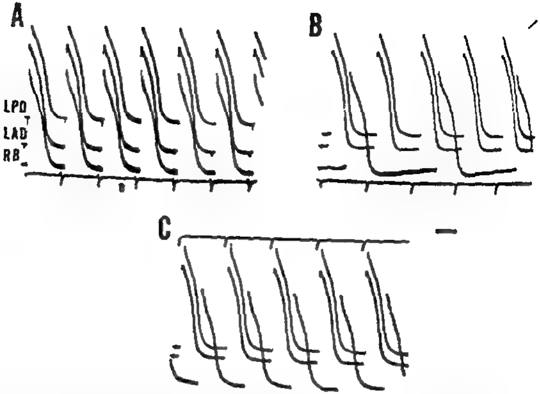

Fig 3 Partial block to the RB after a right sided lesion *Panel A* = the control at BCL of 320 msec *B* = pacing proximal to the lesion at *BCL* of 400 msec *C* = pacing distal to the lesion at BCL of 250 msec. Horizontal calibration line = 200 msec for *A* and *B* and 100 msec for *C*

right sided lesion was made, pacing of the HB proximal to the lesion at the same BCL resulted in partial conduction block of a 2 1 ratio to all three branches A 1 1 conduction to all branches could be again established in this preparation at a BCL of 500 msec As shown in *panel C* 1 1 conduction was resumed to all branches when pacing stimuli were applied to the HB distal to the lesion at a BCL of 250 msec

Discussion

The purpose of the present experiments was to create a model to study the effect of partial transection (about 50 per cent of the cross sectional area) of the nonbranching portion of the HB on impulse conduction to the LPD LAD and RB The results described above indicate that such a lesion did not have much appreciable effect on conduction to the three bundle branches at slow pacing rates below 100 per minute (or BCL s longer than about 600 msec) Conduction disturbances of the bundle branches however, were rate dependent and manifested at faster pacing rates In nine out of all 16 experiments, partial or complete block occurred in all three branches at faster pacing rates regardless of the side of the lesion In the remaining seven experiments, conduction disturbances were observed in the bundle branch on the same side as the les Bailey and associates,[7] using a similar approa as in the present study showed that parti transection of the HB has no effect on impulse conduction to the bundle branches In their expe riments, however, the rate of pacing was rela tively slow with a BCL of 600 msec The prese study, therefore suggests that localized lesions the HB can affect the manner in which impulse conduct to the bundle branches under certa conditions such as the presence of tachycardia c atrial premature beats

At slower pacing rates impulses elicited at the proximal HB could conduct through the uncut portion of HB to all three branches at a ratio of 1 1 The possible explanation is that these impulses propagated down through the uncut portion of the HB and laterally through trans verse crossover connections of the HB and then down to the contralateral bundle branch The existence of functional crossover connections between the longitudinally running HB fibers has been suggested by Bailey and associates[7] and Watt and Pruitt [8] and the anatomical existence of such crossover connections has been demon strated in the HB of the dog and human hearts. In some of the present experiments pacing of the HB proximal to the lesion at faster rates resulted

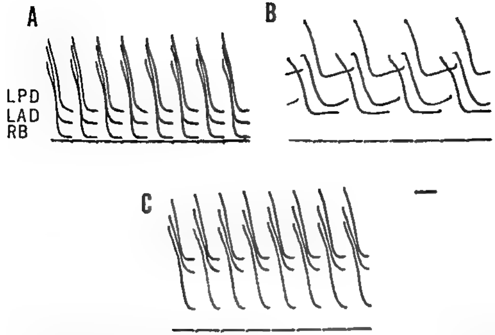

Fig 4 Partial block to all branches (LPD LAD RB) after a right sided lesion *Panel A* = the control at BCL of 250 msec. *B* = pacing proximal to the lesion at BCL of 250 msec *C* = pacing distal to the lesion at BCL of 250 msec. Horizontal calibration line = 200 msec for all panels.

conduction block to all three bundle branches nd such block disappeared when pacing at imilar rates was applied to the HB distal to the sion This suggests that the site of block was tween the two sites of pacing probably at the ncut portion of the HB Although no action otentials were recorded at this site one could robably speculate that decremental conduction ccurred at this site because of slow phase 0 epolarization The observation of selective onduction block to the bundle branch on the ame side as the lesion could probably be xplained by the functional failure of the cross connections In these experiments pacing at lower rates did not cause conduction block in the bundle branch on the same side as the lesion suggesting the function of these crossover connections in the HB at slower pacing rates however conduction block probably occurred in the cross over connections at faster rates of pacing The most probable explanation of such functional failure of the crossover connections would be lower excitability and longer refractory period of this structure At faster pacing rates the phase 0 of action potentials of the uncut portion of HB is expected to become even slower i e a weaker regenerative force for the propagated excitation Therefore the crossover connection fibers which have lower excitability and longer refractory period would fail to be excited

The present findings of conduction block resulting from partial transection of the non branching portion of HB probably have significant clinical implication Arterial blood supply is vital to deep conduction tissues of the heart such as the nonbranching portion of HB which is covered by the thick fibrous connective tissue On the other hand the bundle branches are separated from the ventricular cavities by a relatively thin layer of the endocardium and are able to receive oxygen supply in part from the blood in the cavities [1] This suggests that the HB is possibly more vulnerable to arterial occlusion and poor oxygenation Although fairly fast pacing rates (usually faster than 150 per minute) was required to induce conduction block in the present experiments it should be noted that the HB lesion was limited to a transverse plane and about 50 per cent of the cross sectional area Clinically arterial occlusion may affect a much larger area of the HB or at more strategic points of the crossover connections Therefore the func

tional failure of crossover connections could occur at much slower heart rates Furthermore, the observation of selective conduction block to the bundle branch ipsilateral to the lesion suggests that the longitudinally compartmentarized HB fibers, as demonstrated by James and Sherf,[4] have their functional counterpart under specific conditions It has been believed that conduction disturbances at the bundle branches are due to lesions at the corresponding bundle branch[1,3] The present study provides an additional cause for the development of bundle branch block, i e, a localized lesion in the nonbranching portion of HB

Summary

The present experiments were conducted on isolated dog hearts to demonstrate that conduction disturbances can be induced in the bundle branches by transection of about 50 per cent of the cross sectional area of the His bundle on the right or left side The His bundle, the posterior and anterior divisions of left bundle, and the right bundle were exposed by careful dissection and microelectrode techniques were used to record action potentials from the three bundle branches Pacing stimuli were applied to the nonbranching portion of His bundle proximal and then distal to the site of transection to study the effect of such lesions on impulse conduction to the bundle branches It was demonstrated that conduction to the bundle branches was not affected by such lesions in the His bundle at pacing rates slower than 100 per minute, however conduction disturbances were rate dependent and manifested at faster pacing rates In nine out of all 16 experiments, partial or complete block occurred in all three bundle branches regardless of the side of the lesion In the remaining seven experiments they were observed in the bundle branch on the same side as the lesion It was assumed that conduction disturbances of the bilateral bundle br[illegible] resulted from decremental conduction [illegible] uncut portion of His bundle at the level of le[illegible] and those of the ipsilateral branch from functional failure of transverse crossover con[illegible] tions between the longitudinal His bundle fib[illegible] The results indicate that localized lesions in [illegible] nonbranching portion of His bundle can re[illegible] produce the pattern of bundle branch block [illegible] certain conditions

We are grateful to Rosalyn Rogers for technical a[illegible] and to Oksana Ciupka for preparation of the manuscr[illegible]

REFERENCES

1 Rosenbaum M [illegible] The hemiblocks Diagnostic cri[illegible] and clinical significance Mod Conc Cardiovasc D[illegible] 39 141 1970
2 Rosenbaum M [illegible] Elizari M V Lazzari J O [illegible] G J Levi R J and Halpern M S Intraven[illegible] trifascicular blocks The syndrome of right [illegible] branch block with intermittent left anterior [illegible] posterior hemiblock Am Heart J [illegible] 306 19[illegible]
3 Lenegre J Etiology and pathology of bilateral b[illegible] branch block in relation to complete heart block Pr[illegible] Cardiovasc Dis 6 409 1964
4 James T N and Sherf, L Fine structure of the [illegible] bundle Circulation 44 [illegible] 1971
5 Tse, W W Evidence of presence of automatic fibers [illegible] the canine atrioventricular node Am J Ph[illegible] 225 716 1973
[illegible] Elizari M V Greenspan K and Fisch C Exposure [illegible] the canine proxymal AV conduction system for ele[illegible] physiologic studies J Appl Physiol 34 538 19[illegible]
7 Bailey J C Spear J F and Moore E N Functio[illegible] significance of transverse conducting pathways [illegible] the canine bundle of His Am J Cardiol 34 [illegible]90 19[illegible]
8 Watt, T [illegible] and Pruitt R D Focal lesions in the ca[illegible] bundle of His Circ Res 31 531 1972
[illegible] Hackel [illegible] Wagner G Ratliff N B Cies A, [illegible] Estes E H Anatomic studies of the cardiac cond[illegible] system in acute myocardial infarction Am Heart J 83 77 1972
10 Han J Moe G [illegible] and Molozzi A Transient ventr[illegible] ular conduction disturbances produced by intra arte[illegible] injection of single dose of KCl Circ Res 21 [illegible] 19[illegible]
11 Friedman P L Stewart J R and Fenoglio J J Survival of subendocardial Purkinje fibers after ex[illegible] sive myocardial infarction in dogs Circ Res 33 [illegible] 1973

ft anterior hemiblock simulating anteroseptal yocardial infarction

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ft anterior hemiblock with resultant deviation the initial forces has been reported to simulate iteroseptal myocardial infarction by producing waves on the right precordial leads of the alar electrocardiogram [1] The cases illustrated the literature have shown a qrS pattern in ads V_1 and V_2 We have recently studied a atient with mitral stenosis whose electrocardio am showed a left anterior hemiblock and a qS attern in leads V_1 through V_3 consistent with a rge anteroseptal myocardial infarction Coro ary arteriograms revealed no occlusive lesions nd left ventriculogram and direct observation of he anterior wall motion at surgery were normal n this patient demonstrating that a more latant electrocardiographic appearance of anter septal infarction also may be simulated by block of the anterior fascicle of the left bundle branch Furthermore Frank orthogonal vectorcardio gram failed to show evidence of myocardial nfarction and provided a rational explanation for lectrocardiographic evidence of pseudoinfarc tion

Case report

This 49-year-old white female housewife presented with an eight month history of progressive exertional dyspnea non productive cough, and pressure like chest discomfort occur ring both at rest and on exertion As a child she had had growing pains without definite history of rheumatic fever Mild exertional dyspnea had been present for several years. Four months prior to this evaluation she had been hospital ized at her local community hospital in acute pulmonary

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Table I

	Rest	Exercise
PA	29/11 $\overline{(17)}$	$\overline{(40)}$
LA	$\overline{(11)}$ a=27 v=10	$\overline{(28)}$
LV	1.0/2	
SA	150/85 $\overline{(110)}$	$\overline{(147)}$
CI	2.6	3.5
HR	9?	105
MVA	1 cm	

Left leg supine bicycle e gometer at 50 rpm, no load for 14 minutes.

edema which responded to digitalis and diuretics. Following that hospitalization she had mild ankle edema orthopnea, and several episodes of paroxysmal nocturnal dyspnea leading to her referral for evaluation of mitral valve disease. Past medical history was unremarkable except for 20 years of mild intermittent systemic hypertension not requiring treatment.

Physical examination revealed a thin woman with a blood pressure of 130/?0 pulse 90 and regular in no distress. Jugular venous pressure was normal. Carotid pulses were of normal contour equal and without bruits. The lungs were clear to percussion and auscultation. The cardiac point of maximal impulse was of normal character and duration and was located in the fifth left intercostal space in the mid clavicular line. A right ventricular impulse was also palpable. The first heart sound was loud followed by a normally splitting second sound with normal intensity of the pulmonic component. A prominent opening snap was present along the lower left sternal border and at the apex, occurring 60 [illegible] 80 msec. after the second sound. A Grade II/VI diastolic rumble with presystolic accentuation was present at the apex. The abdom inal examination was unremarkable. There was no peripheral edema and peripheral pulses were unremarkable

The 12 lead scalar electrocardiogram (Fig. 1) revealed normal sinus rhythm at 86 beats per minute with a PR interval of 0 18 sec QRS .08 sec and mean QRS axis of −45 There was evidence of left atrial enlargement. QS complexes were present in leads V through V with ST segment eleva tion. The Frank vectorcardiogram (Fig. 3) revealed a counter clockwise loop in the frontal plane with a mean QRS vector of −30 and a maximum QRS vector of −70 In the horizontal plane a normal counterclockwise loop was present with initial forces directed anteriorly and to the right. The 20 msec. vector

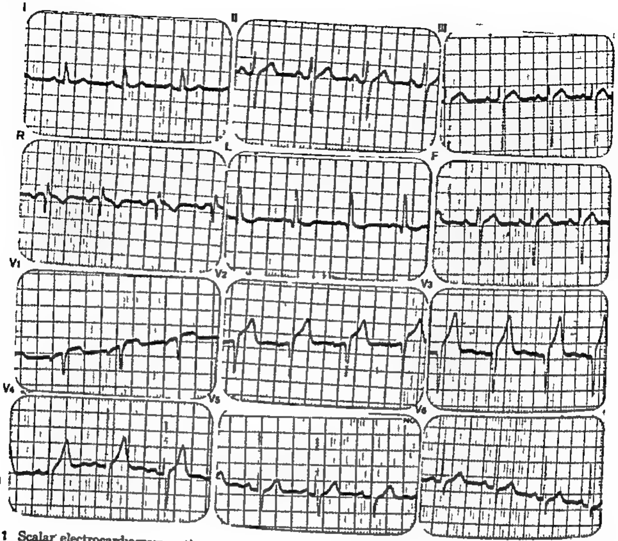

Fig 1 Scalar electrocardiogram with precordial leads recorded in the standard positions (fourth intercostal space)

was directed anteriorly and to the left. In the right sagittal plane initial clockwise forces were directed anteriorly and inferiorly There were late superior forces in the frontal and sagittal planes. Because of the observed discrepancy between routine electrocardiograms and vectorcardiograms precordial leads were repeated with leads V_1 and V in the fifth interspace and in the sixth interspace. The latter showed normal anterior forces and normal R wave progression (Fig 2)

Right heart and transseptal left heart catheterization revealed normal resting right heart pressures, a 9 mm Hg diastolic gradient across the mitral valve and the development of significant left atrial and pulmonary hypertension on mild exercise (Table I) Left heart angiogram (Fig 4) with injection in the left atrium revealed a mildly dilated atrium The left ventricle was normal in size and revealed a completely normal contraction pattern No evidence of anterior wall asynergy was noted in RAO projection Coronary arteriograms revealed normal coronary arteries (Fig 5) with a dominant right system a large first septal branch and hypoplastic left anterior descending

At surgery the left atrium was moderately enlarged the left ventricle was normal in size and contracted normally The mitral valve was severely stenotic with calcium at the posterior medial commissure and shortened and fused chordae tendineae were noted. The valve was replaced with a Starr Edwards prosthesis and the post operative course was uncomplicated.

Discussion

This patient presented with typical features of moderately severe mitral stenosis Additionally she complained of anterior chest discomfort radiating to the neck occurring on exertion and at rest Although her description of pain was not considered typical of angina pectoris, the electrocardiogram seemed clearly to show an anteroseptal myocardial infarction with persistent ST elevation and left anterior hemiblock Thus coexisting coronary artery disease was thought to be present The vectorcardiogram confirmed the left anterior hemiblock but revealed normal anterior forces in the horizontal plane with no evidence of infarction Placement of the precordial leads one interspace below the normal position (i.e., the fifth intercostal space) still revealed QS patterns in V_1 through V_3 However, when these leads were recorded in the sixth intercostal space, normal anterior forces were present The normal coronary arteriograms, normal left ventricular contraction pattern without evidence of anterior wall asynergy and the normal contraction of the

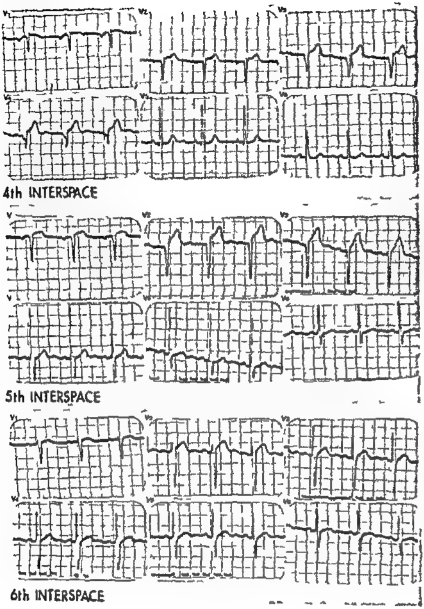

Fig 2. Precordial leads recorded in the two interspaces below the standard positions.

anterior wall of the left ventricle at surgery make the diagnosis of infarction extremely unlikely

Rosenbaum and associates have published examples of block in the anterior fascicle of the left bundle resulting in small q waves in leads V and V_2 followed by small r and larger S waves McHenry and associates[2] published a series of five patients who were without history of angina MI or evidence of overt heart disease with a similar qrS pattern in the right precordial leads They stressed the normalization of the right precordial leads with recording at a lower interspace Vectorcardiograms coronary arteriograms and ventricular angiograms were not available in their patients.

In the presence of left anterior hemiblock the initial forces are directed inferiorly[1] The deviation of these initial vectors results in less anterior orientation of these forces so that the exploring electrode of the precordial electrocardiographic lead system when placed in the standard way at the fourth intercostal space may see the forces directed in an opposite direction and may record a negative potential Thus q or qS waves may be recorded from right precordial leads if the recording plane is above the mean electrical plane

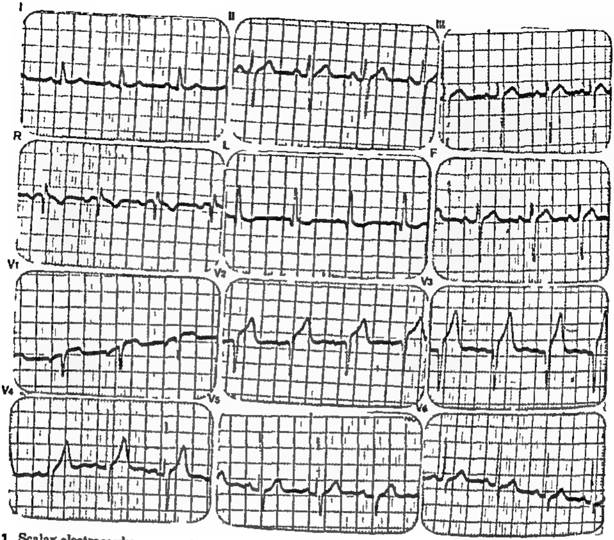

Fig 1 Scalar electrocardiogram with precordial leads recorded in the standard positions (fourth intercostal space)

was directed anteriorly and to the left. In the right sagittal plane initial clockwise forces were directed anteriorly and inferiorly There were late superior forces in the frontal and sagittal planes. Because of the observed discrepancy between routine electrocardiograms and vectorcardiograms precordial leads were repeated with leads V and V in the fifth interspace and in the sixth interspace The latter showed normal anterior forces and normal R wave progression (Fig 2)

Right heart and transseptal left heart catheterization revealed normal resting right heart pressures a 9 mm Hg diastolic gradient across the mitral valve and the development of significant left atrial and pulmonary hypertension on mild exercise (Table I) Left heart angiogram (Fig 4) with injection in the left atrium revealed a mildly dilated atrium. The left ventricle was normal in size and revealed a completely normal contraction pattern No evidence of anterior wall asynergy was noted in RAO projection Coronary arteriograms revealed normal coronary arteries (Fig 5) with a dominant right system a large first septal branch and hypoplastic left anterior descending

At surgery the left atrium was moderately enlarged the left ventricle was normal in size and contracted normally The mitral valve was severely stenotic with calcium at the posterior medial commissure and shortened and fused chordae tendineae were noted The valve was replaced with a Starr Edwards prosthesis and the post operative course was uncomplicated.

Discussion

This patient presented with typical features of moderately severe mitral stenosis Additionally she complained of anterior chest discomfort radiating to the neck occurring on exertion and at rest Although her description of pain was not considered typical of angina pectoris, the electrocardiogram seemed clearly to show an anteroseptal myocardial infarction with persistent ST elevation and left anterior hemiblock Thus coexisting coronary artery disease was thought to be present The vectorcardiogram confirmed the left anterior hemiblock but revealed normal anterior forces in the horizontal plane with no evidence of infarction Placement of the precordial leads one interspace below the normal position (i e., the fifth intercostal space) still revealed QS patterns in V_1 through V_3 However when these leads were recorded in the sixth intercostal space, normal anterior forces were present The normal coronary arteriograms normal left ventricular contraction pattern without evidence of anterior wall asynergy and the ... ion of the

Fig 5 B Left coronary angiogram in LAO position

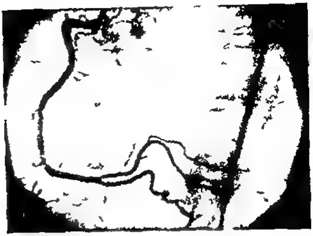

Fig 5 C Right coronary angiogram in LAO position

e anteroseptal leads have also been noted and cently reviewed by Chou [11]

The patient reported here showed no evidence left ventricular hypertrophy clinically angio ·aphically or on either ECG or VCG Formal ulmonary function tests were not performed but either clinical nor laboratory evidence ■ present or obstructive lung disease Septal forces were learly normal by vectorcardiogram and were lso recorded normally in the left precordial leads f the electrocardiogram

Left anterior hemiblock may result in two lectrocardiographic patterns with simulate ante oseptal infarction (1) the qrS pattern in leads V and V_3 suggestive of a small infarct previously reported and (2) a qS pattern in leads V to V consistent with a more massive infarct as documented in this case Recordings obtained from precordial sites at interspaces lower than the tandard sites may provide evidence of inferiorly directed initial forces in these patients thus avoiding an erroneous interpretation

We would like to thank Dr David C Dean and his associates at the Buffalo Veterans Hospital for their independent critical review of the coronary angiograms of this patient.

REFERENCES

1 Rosenbaum, M B Elizari, M V and Lazzari, J O The hemiblocks, Oldsmar Fla., 19 0 Tampa Tracings.
2. McHenry P L., Phillips, J F Fisch C., and Corya B R. Right precordial qrS pattern due to left ventricular hemiblock, Am Heart J ■1 498 1971
3 Rosenbaum, M B The hemiblocks Diagnostic criteria and clinical significance Mod Concepts Cardiovasc Dis. 39 141 19 0
4. Berchunol, A., Barreto E. C., Pedrozza A. The Frank vectorcardiogram in left anterior hemiblock J Electrocardiography 4 116 1971
5 Hugenholtz, F G., Ryan T J Woremer T., and Levine H. D Recognition of anterior wall infarction in patients with left ventricular hypertrophy A study by the Frank vectorcardiogram Circulation 27 386 1963
6. Myers G B QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction I Left ventricular hypertrophy and dilation Circulation 1 844 1950
7 Littman, D The electrocardiographic findings in pulmonary emphysema Am J Cardiol 5 339 1960
8. Fowler N O Jr Westoff R N and Scott R. C The Q wave in precordial electrocardiograms overlying the hypertrophied right ventricle Intracavity leads Circulation 5 441 1952
9 Buja L. M., Khor N B., and Roberts, W C Clinically significant cardiac amyloidosis Am J Cardiol 26 394 19 0
10 Burch, G E., and DePasquale N A study at autopsy of the relation of absence of the Q waves in Leads I AVL V and V to septal fibrosis, Am Heart J 60 336 1960
11 Chou T Pseudo-infarction (non infarction Q waves) Cardiovasc Clinics ■ 199 19,3

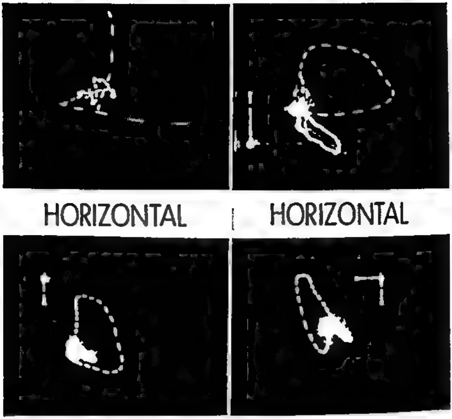

Fig 3 Frank vectorcardiogram with 2 5 msec timing (standardization represents 0 5 mv)

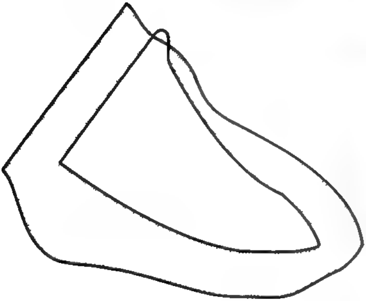

Fig 4 End diastolic and end systolic outlines of the left ventricular angiogram in RAO position

Fig 5 A Left coronary angiogram in RAO projection.

of the ventricles The Frank vectorcardiogram in this patient shows the inferior deviation of the initial forces and clearly does not meet criteria for an anteroseptal infarction in that the initial forces up to the 10 msec vector are oriented anteriorly and to the right and the 20 msec vector is anterior and to the left rather than posterior

Electrocardiographic patterns simulating anteroseptal infarction are well known to occur in patients with left ventricular hypertrophy[3,4] marked clockwise rotation as in chronic obstructive lung disease[7,8] and infiltrative diseases of the myocardium as in amyloidosis[9] Septal fibrosis may result in absent right precordial R waves and absent Q waves over the left precordium[10] A wide variety of non infarction Q waves in other than

ieved by 5 to 10 minutes of rest. The patient had had no ardiac symptoms and, at the time of our examination id no dyspnea with exertion or at rest no edema, ss, or syncope, and no previous knowledge of a heart ur She smoked one pack of cigarettes daily and other er hypertension, had no risk factors for coronary artery

e.

sical examination disclosed height, 170.2 cm weight, ilograms, pulse, 0 beats per minute and blood pressure 0 mm. Hg sitting and 140/96 standing The patient's trunk (Fig. 1) and extremities including the digits were ed with innumerable solid and cystic neurofibromas. In a reas these nodular lesions were confluent, and especially ment lesions occurred on the nipples. A relatively small er of *café-au lait* spots were present on the trunk and mities. The largest of these on the medial aspect of the midthigh, measured 3 5 by 2 5 cm Clusters of small *café it* spots were also present in both axillae There were a mall nodules on the conjunctivae bilaterally but there no other lesions on scalp nails, or mucous membranes. nduscopic examination revealed grade 1 arteriolar owing and sclerosis. All peripheral pulses were palpable the resting carotid pulse contour was normal. The jugular us pressure was normal. The lung fields were clear The iac apical impulse was palpable in the fifth intercostal e in the midclavicular line and had a normal contour The and second heart sounds were normal A Grade 2/6 olic ejection murmur was present along the lower left nal border The intensity of the murmur remained hanged during the Valsalva maneuver but it disappeared passive leg raising and during squatting. The murmur eased to Grade 4/6 when the patient rapidly returned to upright position from the squatting position The murmur ilarly increased with amyl nitrite inhalation which also sed the carotid impulse to become bifid.

There were no other somatic developmental anomalies and re was no hearing deficit.

Laboratory data included hemoglobin, 16 0 Gm./100 ml. kocyte count, 10 100 cells with a normal differential and nalysis, normal. Other laboratory investigations that were rmal included serum potassium fasting plasma glucose olesterol, triglycerides, creatine phosphokinase serum itamic oxalacetic transaminase lactate dehydrogenase inary vanillylmandelic acid homovanillic acid and meta phrines.

Chest roentgenograms and cardiac fluoroscopy revealed no lcification of valves or coronary arteries. The electrocardio am showed normal sinus rhythm and only minor repolariza on changes in Leads I and aVL. The vectorcardiogram was ormal. A hypertensive excretory urogram and an isotope nogram were normal.

On the basis of the physical examination idiopathic hyper rophic subaortic stenosis was strongly suspected and, ecause the echocardiogram was suggestive of idiopathic ypertrophic subaortic stenosis but not of diagnostic quality ardiac catheterization was performed. The hemodynamic ummary is shown in Table I During catheterization the ost premature ventricular contraction response was vari ble but a gradient from left ventricle to femoral artery of up o 31 mm. Hg was seen. The Valsalva maneuver and amyl itrite inhalation did not produce a gradient. However Isuprel nfusion at 0 08 μg per kilogram per minute elicited a gradient

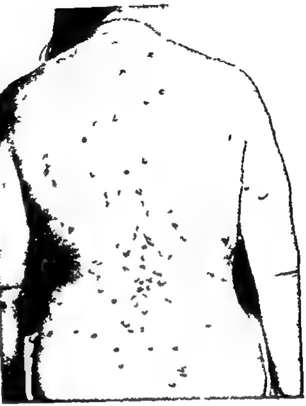

Fig 1 Multiple neurofibromas of variable size and confluence. Note café au lait spots below left scapula, in midlumbar area, and over right hip

from the left ventricular sinus to the left ventricular outflow tract and caused the arterial contour to become bifid (Fig 2) Simultaneous right and left ventricular angiograms showed the septum, as viewed on edge to be thickened with a wide base as has been described in idiopathic hypertrophic subaortic stenosis.

Discussion

In early histochemical studies of surgically resected left ventricular septal muscle from patients with idiopathic hypertrophic subaortic stenosis excessive numbers of sympathetic nerve fibers and amounts of catecholamines were found This gave objective support to the hypothesis that a disordered sympathetic supply is involved in the pathogenesis of this disease[4] However later investigators demonstrated similar changes in hypertrophied left ventricular muscle from other causes[5, 6] indicating the nonspecific nature of these changes. Recently Van Noorden and associates[7] observed an apparent increase in formaldehyde induced fluorescence of norepinephrine in idiopathic hypertrophic subaortic stenosis but pointed out that this could not be

Idiopathic hypertrophic subaortic stenosis associated with cutaneous neurofibromatosis Report of a case

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The numerous studies of patients with idiopathic hypertrophic subaortic stenosis have provided copious information about clinical manifestations, hemodynamics, echocardiographic and angiocardiographic appearances prognosis, possible genetic factors, and pathology of this not so rare disease However, the primary pathogenesis remains unexplained The observation of marked hemodynamic changes in patients with idiopathic hypertrophic subaortic stenosis during catecholamine manipulation has led to speculation that the basis of the disease is a disturbance in the sympathetic nerve supply of the heart [1,2] Such speculation was intensified by Polani and Moynahan's[3] description of the syndrome of idiopathic hypertrophic subaortic stenosis with lentigines and suggestion of a common neuroectodermal defect to account for both lesions Others have confirmed the association of idiopathic hypertrophic subaortic stenosis and lentigines [4] In addition, Goodwin[5] has observed a patient with idiopathic hypertrophic subaortic stenosis and pheochromocytoma[5] and we have observed a patient with idiopathic hypertrophic subaortic stenosis and tuberous sclerosis [6] Such observations provide support for the hypothesis that a heritable neuroectodermal defect is the basis of idiopathic hypertrophic subaortic stenosis and the various extracardiac lesions that are often associated with it

We now report another observation consistent with this hypothesis the case of a woman in whom idiopathic hypertrophic subaortic stenosis was associated with cutaneous neurofibromatosis

Case report

A 44 year old white woman came to the Mayo Clinic in November 1974 for consultation concerning her headaches hypertension, and skin lesions

The headaches first began at age 39 and were by history tension myalgias A normal neurologic evaluation and a negative cervical spine x rays supported this clinical diagnosis

Hypertension was discovered 7 years ago during a routine physical examination elsewhere. Laboratory investigation for secondary causes were negative at that time Her blood pressure has been easily controlled by methyclothiazide and deserpidine (Enduronyl Forte) and no secondary complications have arisen

She first became aware of her skin lesions at age 22, when nodules appeared on her face They have progressively increased in number and in size to involve her entire face trunk and extremities. Biopsies of the skin lesions confirmed the clinical diagnosis of neurofibromatosis.

The patient's mother has similar lesions that were diagnosed elsewhere as "von Recklinghausen's disease" when she was in her 40's. The father had normal skin but died at age [illegible] of pneumonia The patient has two siblings a brother who had normal skin and died of stomach cancer at age 46 and a sister who is 46 years old and in good health The patient had four children the oldest son and daughter ages 23 and [illegible] years, respectively have nodular and pigmented skin lesions that were diagnosed elsewhere as von Recklinghausen's disease" another son age 15 years has normal skin the youngest child a daughter died of meningitis at the age of [illegible] months. The patient had a spontaneous second trimester miscarriage and a stillborn daughter during her second marriage None of the first degree relatives are known to have heart disease deafness or somatic development anomalies.

During the previous 2½ months the patient had experienced five episodes of severe knifelike retrosternal pain that occurred with strenuous exertion The pain did not radiate and

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pp 369 31

ble I Results of cardiac catheterization

	Resting (mm. Hg)	*Isuprel infusion†‡ (mm. Hg)*	*Withdrawal (during Isuprel infusion)‡ (mm. Hg)*
moral artery	154/86	134/24	
cending aorta			148/90
ft ventricular base			152/2-8
ft ventricular apex	147/2-8	288/2 12	282/2-8
edge	12/4		
ain pulmonary artery	25/7		
ight ventricle	31/0-4		
ight atrium	10		

ardiac inde 2.65 L. per minute per square m ter heart rate 66.
ardiac inde 6.0 L. per minute per square meter heart rate 145
At 0.08 μg per kilogram per minute

re the observations of Goodwin concerning a atient with idiopathic hypertrophic subaortic tenosis and pheochromocytoma and our experi nce with a patient with idiopathic hypertrophic and tuberous sclerosis [6] in both ases, the extracardiac manifestations could be as neuroectodermal in nature Second of a patient in whom idiopathic ypertrophic subaortic stenosis is associated with cutaneous neurofibromatosis is an additional xample of the association of the cardiac lesions with a neuroectodermal disorder Histologi ally the lesions of idiopathic hypertrophic subaortic stenosis, neurofibromatosis tuberous sclerosis, and pheochromocytoma can be regarded as hamartomas or tumors of developmental origin.

Many cases of idiopathic hypertrophic subaor tic stenosis are familial and have an autosomal dominant pattern of inheritance [3] When the idiopathic hypertrophic subaortic stenosis is part of the Leopard syndrome this pattern of inher itance is even more likely to be present [2] Simi larly neurofibromatosis and tuberous sclerosis usually show the autosomal-dominant pattern of inheritance [1] Familial pheochromocytoma is not common but when it occurs it is sometimes associated with neurofibromatosis and usually shows an autosomal-dominant pattern of inherit-ance. Thus, it is reasonable to postulate a heritable defect of neuroectodermal development in the pathogenesis of idiopathic hypertrophic subaortic stenosis lentiginosis, pheochromocy toma, tuberous sclerosis, and neurofibromatosis

Table II Some clinical manifestations of neurofi bromatosis

Alimentary
- GI hemorrhage

Cardiovascular
- Aortic constriction
- Idiopathic hypertrophic subaortic stenosis
- Renal artery dysplasia

Endocrine
- Hypoglycemia
- Pheochromocytoma
- Precocious puberty

Musculoskeletal
- Bone cysts
- Fractures
- Asymmetrical growth
- Scoliosis

Nervous system
- Acoustic neuroma
- Brain tumor (hydrocephalus)
- Nerve root tumor
- Spinal cord tumor

Ocular
- Glaucoma
- Retinal detachment
- Retinal phakoma

Skin
- *Cafe au lait spots*
- Nodular lesions
- Plexiform neuroma

Urinary
- Bladder tumor

The mutant autosomal gene responsible for neurofibromatosis has pleiotropic effects that is, it has diverse clinical manifestations that may occur singly or in many different combinations (Table II) We have added idiopathic hyper trophic subaortic stenosis to this list. It is usual clinical practice to regard the nodular or pigmented cutaneous lesions as essential for the diagnosis of neurofibromatosis. However if some patients who have inherited the mutant gene have only cutaneous manifestations, it may be that other patients who inherit the same mutant gene might have one or more of the visceral or somatic anomalies without cutaneous manifesta tions. To test this hypothesis, other clinical mani festations of neurofibromatosis should be sought among relatives of patients with idiopathic hyper trophic subaortic stenosis. We also suggest that any patient with a neuroectodermal disorder and an indeterminate cardiac murmur should be eval uated for idiopathic hypertrophic subaortic stenosis.

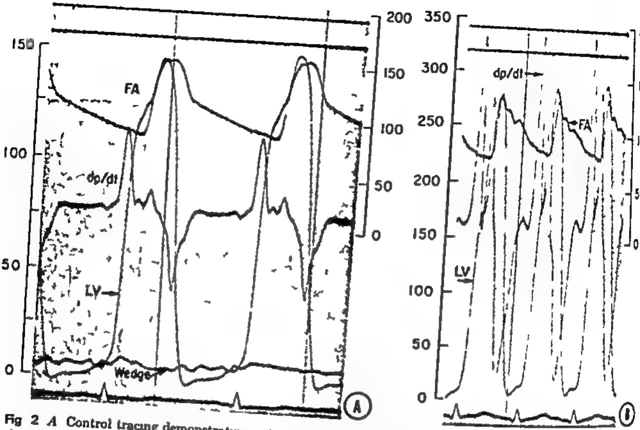

Fig 2 *A* Control tracing demonstrating patient's hemodynamics at rest. Left ventricular recording (*LV*) was obtained with catheter positioned in left ventricular sinus There is no gradient from *LV* to femoral artery (*FA*) recording and *FA* contour is normal. *B* Recording obtained during Isuprel infusion (0 08 μg per kilogram per minute) with left ventricular catheter positioned at left ventricular sinus. Due to elevated left ventricular pressure, it is now being recorded at lower sensitivity thus accounting for change in pressure scale from control tracing. Note that Isuprel infusion has elicited a 154 mm Hg gradient from *LV* to *FA* *FA* also demonstrates bifid contour as seen in idiopathic hypertrophic subaortic stenosis.

distinguished from the autofluorescence of the connective tissue that is demonstrably increased in idiopathic hypertrophic subaortic stenosis Hence, Van Noorden and associates concluded that more detailed studies, with combined emission and absorption techniques were necessary to determine how much of the increased fluorescence was secondary to catecholamines and how much was secondary to increased connective tissue

Other evidence for possible neural pathogenesis for idiopathic hypertrophic subaortic stenosis was introduced by Moynahan[12] in 1962 when he reported the association of lentigines with idiopathic hypertrophic subaortic stenosis Subsequent clinical studies by Polani and Moynahan[3] and by others[4] led to the recognition of a more complex syndrome of idiopathic hypertrophic subaortic stenosis associated with lentigines nerve deafness, shortness of stature, mild mental subnormality, and other anomalies of development, this is sometimes called the 'Leopard syndrome" Polani and Moynahan[3] postulated that a neuroectodermal defect in embryogenesis accounted for the cardiac cutaneous, and other manifestations of this syndrome

Some support for a common pathogenic basis for the heart lesion and lentigines comes from observations of Somerville and Bonham Carter of a correlation between an increase in the number of skin lesions and progression of the associated idiopathic hypertrophic subaortic stenosis However, the nature of this embryogenic link between the cardiac and the extracardiac manifestations has not yet been demonstrated For example in neither our patient nor the patients reported by Polani and Moynahan[3] has an excessive production of catecholamines been demonstrated by standard blood and urinary assays.

Nevertheless further clinical observations have led us to believe that attempts to identify the postulated primary defect affecting neuroectodermal development should continue First there

table angina pectoris

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ectrum of symptomatic manifestations of mic heart disease lies between the well ed diagnosis of stable angina pectoris on the hand and acute myocardial infarction (AMI) he other A variety of terms has been used in attempt to describe this group of manifesta s. Preinfarction angina acute coronary fficiency[2] intermediate coronary syndrome[3] endo angina[4] and unstable angina are the t frequently employed Each tends to focus different aspects of the symptomatology The rts concerning these clinical states are diffi to evaluate and compare because of the nsistent nomenclature and patient selection purpose of this communication is first to mpt a more precise definition of this spectrum l second to evaluate the published reports in t of this definition

The predominant manifestation of all syn mes falling within this spectrum is that of hemic cardiac pain The diagnosis is therefore gely based on history The term unstable gina pectoris, advocated by Conti and asso tes[5] is perhaps the most simple inclusive and criptive which may be applied to this spec m They defined unstable angina pectoris as syndromes of chest pain interposed between ble angina pectoris and myocardial infarction 1) They distinguish three groups (1) Angina on effort of recent onset (past 4 weeks) (2) Angina on effort with a changing pattern The patient with this pattern has usually had typical stable angina and now has increasing frequency or severity of ischemic cardiac pain (3) Angina at rest The patient with this condition requires no stress to provoke episodes of ischemic cardiac pain The pain must arbitrarily last 15 minutes or more Most authors stress a recurrent pain pattern Important subgroups within Group 2 or Group 3 are those patients with a history of previous angina or of myocardial infarction such a history appearing to significantly worsen prog nosis. The designation of acute coronary insuffi ciency is generally reserved for Group 3 patients in most reports employing this term

There are two important considerations in management (1) the syndrome may presage acute myocardial infarction or sudden death (2) the syndrome may itself be the manifestation of a (usually small) myocardial infarction Studies have shown that up to 60 per cent of patients with acute myocardial infarction have had prodromal chest pain from 1 day to 3 months prior to their infarction[7] The prodromes are those defined in Groups 1 2 and 3 and thus allow the recognition of a population of patients at risk of myocardial infarction Since 60 per cent of deaths from myocardial infarction occur before the patient reaches hospital the identification and intensive management of patients likely to develop myocardial infarction should provide consid erable salvage Certain patients within the clin ical spectrum of unstable angina particularly Group 3 may represent a problem in deciding whether a myocardial infarction has occurred It is therefore necessary to include in the definition of unstable angina pectoris laboratory evidence by which acute myocardial infarction may be excluded Serum enzymes (SGOT LDH CPK)

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Summary

Although idiopathic hypertrophic subaortic stenosis has been studied extensively, its etiology has remained elusive Recent reports of its association with neuroectodermal syndrome suggest that at least some cases may be the manifestation of a heritable defect of neuroectoderm Consistent with this hypothesis, we report a case of idiopathic hypertrophic subaortic stenosis associated with neurofibromatosis

Addendum

Since submission of this article, the report of Gerbaux and associates[16] has been brought to our attention

REFERENCES

1 Goodwin J F Shah P M Oakley C M Cohen J Yipintsoi, T and Pocock W The clinical pharmacology of hypertrophic obstructive cardiomyopathy *in* Wolstenholme G E W and O Connor M editors Ciba Foundation symposium on cardiomyopathies Boston 1964 Little Brown & Company pp 189 213
2. Linden R. J Related physiology of cardiac contraction *in* Wolstenholme G E W and O Connor M editors Ciba Foundation symposium on cardiomyopathies Boston 1964 Little Brown & Company pp 100 113
3 Polani, P E and Moynahan E J Progressive cardiomyopathic lentiginosis Q J Med 41 205 1972
4 Somerville J and Bonham Carter R E The heart in lentiginosis Br Heart J 34 58 1972.
5 Goodwin J F Prospects and predictions for the cardiomyopathies, Circulation 50 210 1974
6 Brandenburg R. O Tajik, A J Giuliani E R Weidman W H Ritter D G Davis G D and McGoon D C Congenital cardiovascular lesions associated with idiopathic hypertrophic subaortic stenosis (IHSS) (abst.) Circulation 46(Suppl. 2) 134 1974
7 Redwood, D R., Scherer J L., and Epstein, S E Biventricular cineangiography in the evaluation of patients with asymmetric septal hypertrophy Circulation 49 1116, 1974
8. Pearse A. G E The histochemistry and electron microscopy of obstructive cardiomyopathy *in* Wolstenholme G E W and O Connor M., editors Ciba Foundation symposium on cardiomyopathies, Boston, 1964 Little Brown & Company pp 132 164
9 Snijder, J de Jong J., and Meijer A. E F H. Histopathological enzyme-histochemical and electron-microscopical observations in hypertrophic obstructive cardiomyopathy Pathol. Microbiol (Basel) 35 81 1970
10 Kristinsson, A. Van Noorden S., Olsen, E. G J Goodwin J F., McDonald L. Oakley C and Somerville, J Hypertrophy and obstruction of outflow tract of left ventricle, Br Heart J 32 554 1970.
11 Van Noorden S Olsen E G., and Pearse A. G. E Hypertrophic obstructive cardiomyopathy A histological histochemical and ultrastructural study of biopsy material, Cardiovasc. Res. 5 118 1971
12. Moynahan E J Multiple symmetrical moles, with psychic and somatic infantilism and genital hypoplasia First male case of a new syndrome Proc. R. Soc. Med 55 959 1962
13. Epstein, S E Henry W L. Clark C E Roberts, W C. Maron B J., Ferrans, V J Redwood, D R, and Morrow A. G Assymmetric septal hypertrophy Ann Intern Med 81 650 1974
14 Ford F R. Diseases of the nervous system in infancy childhood and adolescence ed 6 Springfield, Ill., 1973 Charles C Thomas Publisher
15 Hermann, H. and Mornex R Human tumours secreting catecholamines Clinical and physiopathological study of the pheochromocytomas, New York, 1964 Pergamon Press.
16. Gerbaux A Belfante M and Hiltgren M Myocardiopathie obstructive syndrome de Turner-Ullrich et maladie de Von Recklinghausen Ann. Med Interne (Paris) 125 641 1974

able angina pectoris

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Medic l Research Council F llow

Medical Research Co cil Student F llowsh (Med c l Stude t, cGill Univers ty)

Summary

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2 Linden R J Related physiology of cardiac contraction *in* Wolstenholme G E W and O Connor M editors Ciba Foundation symposium on cardiomyopathies Boston 1964 Little Brown & Company pp 100-113

3. Polani, P E., and Moynahan E J Progressive cardiomyopathic lentiginosis, Q J Med 41 205, 1972

4 Somerville J and Bonham Carter R E The heart in lentiginosis, Br Heart J 34 58 1972

5 Goodwin J F Prospects and predictions for the cardiomyopathies, Circulation 50 210 1974

6 Brandenburg R O Tajik A J Giuliani, E R Weidman W H., Ritter D G Davis G D and McGoon D C Congenital cardiovascular lesions associated with idiopathic hypertrophic subaortic stenosis [illegible] (abst.), Circulation 46(Suppl. 2) 134 1974

7 Redwood, D R Scherer J L., and Epstein, S E Biventricular cineangiography in the evaluation of patients with asymmetric septal hypertrophy Circulation 49 1116, 1974

8. Pearse A. G E. The histochemistry and electron micros copy of obstructive cardiomyopathy *in* Wolstenholme G E. W and O Connor M., editors Ciba Foundation symposium on cardiomyopathies, Boston, 1964, Little Brown & Company pp 132 164

9 Snijder J., de Jong J., and Meijer A. E. F H. [illegible] pathological, enzyme-histochemical and electron-micro scopical observations in hypertrophic obstructive cardiomyopathy Pathol. Microbiol (Basel) 35 81 1970

10 Kristinsson, A., Van Noorden S., Olsen, E. G. J Goodwin J F McDonald L. Oakley C., and Somerville J. Hypertrophy and obstruction of outflow tract of left ventricle, Br Heart J 32 554 1970

11 Van Noorden, S., Olsen E. G., and Pearse, A. G. E. Hypertrophic obstructive cardiomyopathy A histological, histochemical, and ultrastructural study of biopsy material, Cardiovasc. Res. 5 118, 1971

12. Moynahan E. J Multiple symmetrical moles, with psychic and somatic infantilism and genital hypoplasia First male case of a new syndrome, Proc. R. Soc. Med 55 959 1962.

13. Epstein S E., Henry W L., Clark, C E., Roberts, W C., Maron B J., Ferrans, V J Redwood, D R., and Morrow A. G Assymmetric septal hypertrophy Ann Intern Med 81 650 1974

14 Ford F R. Diseases of the nervous system in infancy, childhood and adolescence ed 6 Springfield, Ill, 1973 Charles C Thomas, Publisher

15 Hermann, H and Mornex R Human tumours secreting catecholamines Clinical and physiopathological study of the pheochromocytomas, New York, 1964 Pergamon Press.

16. Gerbaux A., Belfante M and Hiltgren, M. Myocardiopathie obstructive, syndrome de Turner Ullrich et maladie de Von Recklinghausen Ann Med. Intern (Paris) 125 641 1974

Natural history of unstable angina

Year	Name of syndrome	Avg age	No of patients	Group I	Group II	Group III	Acute: Time interval (mo)	Acute: MI	Acute: Death	Follow up: Time interval (mo)	Follow up: MI	Follow up: Death
1956	Changing patterns of angina pectoris		158		158		2	39% (62/1[illegible]8)	32% (51/158)			
1960	Impending MI	57	15		8	7	1.5	80% (12/15)	60% (9/15)	6	94% (14/15)	73% (11/15)
1961	Acute and subacute coronary insufficiency	56	50			50	2	22% (11/50)	16% (8/50)	6		30% (15/50)
1961	Intermediate coronary syndrome		251			[illegible]	3	37% (93/251)	0.8% (2/251)			
1964	Preinfarction syndrome	54	156			156	3	49% (77/156)	24% (37/156)			
1972	Preinfarction (unstable) angina	56	140		140		3	21% (29/140)	10% (14/140)	[illegible]		18% (25/140)
	Subgroup with pain after 48 hr	57	54		54		3	35% (19/54)	26% (14/54)	[illegible]		43% (23/54)
1972	Unstable angina	56	47		47		1	8% (4/47)	8% (4/47 1 MI 1 surgery 2 others)	14		25% (12/47)
1971	Acute coronary insufficiency	62	100			100	1	[illegible]% (7/100)	1% (1/100)	12	20% (20/100)	15% (13/88)
	Subgroup with pain after 12 hr		[illegible]			36	1	17% (6/36)	0			
1972	Unstable angina		167	88	9		3	15.5% (26/167)	1.8% (3/167)			
	Subgroup requiring hospitalization		45		45		3	20% (9/45)	2.2% (1/45)			

l edema as a consequence of ischemia It is ssible that edema formation could lead to the atinuation of ischemia in a region The benefi il effects of mannitol on myocardial perform ce following a period of ischemia might be the ult of a decrease in edema Another factor nich may be of importance is excess beta mpathetic tone The effectiveness of propran ol in preventing angina pectoris and its ability limit infarct size[20] suggest a role for the beta mpathetic receptor in the transition from ngina to infarction Maroko and Braunwald ave described a series of interventions which mit infarct size An understanding of the mech nisms by which these interventions act may shed ght on how the reversible anginal attack rogresses to unstable angina or finally to nyocardial infarction The primary role of the oronary thrombus as the cause of infarction has een challenged by Roberts and Buja They have shown that the incidence of thrombosis increases with time between infarction and death suggesting that the thrombus is a consequence rather than the cause of the infarct A more complete understanding of the pathophysiology of this syndrome will lead to a more rational approach to its therapy

Natural History

The outcome of the various syndromes of unstable angina has been the object of several studies (Table I) The data from the studies of Levy[22] Beamish and Storrie[24] Wood[25] and Vakil are from patients who received no long acting nitrates no anticoagulants and no β blocking agents Reduction in activities and nitroglycerin were generally employed. The data from the studies of Gazes[28] Watkins Krauss[30] and Fulton[7] and associates are from patients treated with varying regimens utilizing long acting

may rise only minimally (under 50 per cent) and electrocardiograms (ECG) may not show new Q waves or manifestations of subendocardial infarction (ST and T wave changes are frequent and represent ischemia) In subsequent discussion we will adhere to this definition and attempt to evaluate the published literature within this context

Pathophysiology

Studies of the hemodynamic changes occurring in patients during unstable angina have appeared in the literature Cannom and associates[9] recognized three groups of patients based on the particular hemodynamic changes which preceded or were associated with the attacks of pain These changes were an increase in heart rate, an increase in both heart rate and brachial artery pressure or, third, no increase in heart rate but an increase in brachial artery pressure accompanied by an increase of pulmonary artery pressure They suggested that a variety of precipitating factors was present but that in any one patient the pattern of pain and the precipitating factors were always the same Maseri[10] investigated a group of patients in whom the clinical syndrome of unstable angina was present associated with S T segment elevation in the ECG analogous to that described by Prinzmetal and associates[11] They observed that the initial event was an increase in negative dP/dt as measured in the left ventricle, then a decrease in positive dP/dt and finally an increase in left ventricular end diastolic pressure all reflecting acute deterioration of left ventricular function and occurring before the appearance of the ECG changes or the complaint of pain When coronary angiography was performed all patients manifested coronary artery spasm in the region indicated by the S T segment vector They interpreted their observations to mean that the primary event was myocardial, i e spasm within a vessel Cannom and associates,[9] in studies of patients without S T segment elevation, supported the hypothesis proposed by Gorlin[12] that the precipitating factor for the anginal episodes was extracardiac It appears from the pathophysiologic viewpoint that several mechanisms may be involved in this syndrome

Coronary angiography has been performed on patients with unstable angina revealing single vessel disease in approximately 30 per cent, two vessel disease in 30 per cent, three vessel disease in 30 per cent, and normal coronary remaining 10 per cent[9,10,40,51] These are not dissimilar from those found in pat with chronic stable angina[13] It therefore ap that the syndrome is not the particular anatomic pattern of coronary d

Maseri[14] has observed regional m blood flow using ^{133}Xe both during sponta angina and during pacing induced an patients with coronary artery disease T observed that during a pain period a regi reduced blood flow appeared In our laborat we observed that coronary perfusion sometimes decreased during pacing induced na[15]—a phenomenon which we refer to as onary steal"[16] The sequence of events to this regional decrease in coronary perf may be as follows Stress results in increa myocardial oxygen demand Regions of dium with adequate coronary or collateral flow increase their flow by appropriate autore lation A region perfused by a coronary art which is severely obstructed, or in spasm can increase its flow because it is already maxim dilated Vasodilatation occurring in healt regions may lead to a fall in perfusion which may be detrimental to the ischemic reg This decrease in pressure may decrease the p sure available to perfuse the collaterals from t normal region to the abnormal region Second decreased pressure gradient will be present the coronary artery obstruction, so that d pressure falls, leading to a selective decrease endocardial blood flow as a consequence of end cardial vessel closure and relative epicard shunting[16] This maldistribution is the result differences in vascular impedence of the tr layers Associated with endocardial hypoperfu sion a localized tissue acidosis ensues in th ischemic region, with a cessation of contractilit If the precipitating cause is withdrawn normal autoregulatory tone is re established coronary perfusion pressure distal to the obstru tion will increase and blood flow distribution w return to its previous pattern However, if th precipitating cause persists, a series of events the ischemic region may occur which over period of time may lead to myocardial

The pathophysiologic events leading to m cardial infarction are largely unknown but are several possible contributing factors Leaf has called attention to the appearance of myoca

II Anticoagulant therapy of unstable angina pectoris

Year	Name of syndrome	No of patients		Group I	Group II	Group III	Acute: Time interval (mo.)	Acute: MI	Acute: Death
1949	Impending MI	Control	0						
		Anticoagulant	318		318		1	6.6% (21/318)	1.5% (5/318)
1960	Impending MI	Control	15		8	7	1.5	80% (12/15)	60% (9/15)
		Anticoagulant	85		47	38		2.4% (2/85)	0
1961	Acute and subacute coronary insufficiency	Control	50			50	2	22% (11/50)	16% (8/50)
		Anticoagulant	100			100		3% (3/100)	2% (2/100)
1964	Preinfarction syndrome	Control	156			156	3	49% (77/156)	24% (37/156)
		Anticoagulant	190			190		36% (69/190)	9.5% (18/190)

acute myocardial infarction rate has fallen ply and in the recent studies is low—ranging 1 7 per cent (1 month) to 15.5 per cent (3 .ths) The early mortality rate is also low ging from 1 per cent (1 month) to 1 8 per cent months) Second, there appear to be two ips of patients at increased risk—those with asting pain at bed rest[24, 30] and those whose table angina is superimposed on stable angina revious myocardial infarction [8, 30] Gazes and ociates demonstrated that those patients with sistent pain are generally those with previous ina or myocardial infarction The increased of death seen early in these patients persists oughout a 10 year follow up[30]

A consensus of opinion has emerged that Group patients have a lesser incidence of acute ocardial infarction and death than Group 2 or patients, but in fact, none of the published dies was designed to reveal a stratified prog sis based upon the individual syndromes of stable angina.

erapy

Anticoagulation Four major trials of anticoag ation therapy in unstable angina (Table II) the ost recent reported in 1964 unanimously nclude that anticoagulation is efficacious but ot one of them meets the criteria which are sential for such studies[2] and the conclusions ached must therefore be questioned. Similar eficiencies weaken the conclusions of studies of he use of anticoagulants in established myocar dial infarction.[3, 36]

Beamish and Storrie [4] reported the outcome of 00 patients who presented with unstable angina (Group 2 or 3) between 1949 and 1957 Eighty five patients were hospitalized put at bed rest, and given anticoagulants. The 15 patients who were not hospitalized because of noncompliance or lack of beds were not anticoagulated and were considered to be control subjects. During the 6 weeks after diagnosis of acute coronary insufficiency" two of the 85 anticoagulated patients suffered acute myocardial infarction and none died. Of the 15 untreated patients 12 had infarction (all of them outside of hospital) and nine died. Krauss and associates[39] have observed that bed rest alone may play an important role in the prevention of myocardial infarction in unstable angina. The denial of bed rest and hospital nursing care would be expected to have an adverse effect on the "controls in the study of Beamish and Storrie Their conclusion that "prompt administration of anticoagulants appears to influence the outcome favorably is not justified, in view of the inadequacies of the study

Wood[5] studied 150 patients with unstable angina (Group 3) between 1947 and 1957 All were put at bed rest, of whom 100 received anticoagulants and 50 did not. During the 2 months after diagnosis, myocardial infarction occurred in 3 per cent and death in 2 per cent of the treated patients and in respectively 22 and 16 per cent of the control patients. The controlled phase of the study lasted for only the first 40 patients, though even here the treatment regimen was not randomly assigned or double blind When there appeared to be an advantage to the first 20 patients who were anticoagulated there was no further attempt to alternate treated and "con

nitrates, anticoagulation, and β blocking agents, and thus are not truly natural history studies but reflect rather the outcome of currently popular therapy

In the studies carried out before 1970, unstable angina was followed by acute myocardial infarction in from 21 to 80 per cent of cases and by death in from 1 to 60 per cent However, the high rates of early acute infarction and death have fallen sharply in more recent studies in which the ranges are from 7 to 15 and 1 to 2 per cent, respectively The reduction of infarction rate may in part be a result of the changing definition of unstable angina, which now includes patients who are early in their ischemic history Thus, Fulton and associates[7] included in their study a large number of patients whose only symptom was the onset of angina during the preceding 4 weeks (Group 1) a group not included in any of the earlier studies However, Krauss and associates[30] looked only at Group 3 patients, yet the incidence of acute myocardial infarction was only 7 per cent in one month This low infarct and mortality rate may have been influenced by the exclusion of any patient with congestive heart failure from the study The reduction in infarction rate is likely the result of greater awareness of the significance of the syndrome and an increased tendency to put patients in hospital or at bed rest at home The utilization of anticoagulation and β blockade may also be a factor, and will be discussed below The reduction of mortality rate may reflect the trend to admit these patients to hospital and to monitor them if a myocardial infarction occurs thereby reducing primary arrhythmic deaths

The study of Fulton and associates[7] is the most representative of a community experience The male patients of a large group of general practitioners in Edinburgh were studied Patients entered the study if they developed unstable angina Groups 1, 2 or 3, but were hospitalized only if they fell into Group 2 or Group 3 or if myocardial infarction was suspected No anticoagulation was used Of 167 patients 15 5 per cent developed documented or presumed acute myocardial infarction and 1 8 per cent died within 3 months—the majority of events occurring within 4 weeks Of the 167 patients, 45 were hospitalized, and the acute myocardial infarction rate (20 per cent) and mortality rate (2 2 per cent) in this group were only slightly higher than in the total group This study is still in progress

The study of Krauss and associates[30] best repre-
sents hospital management of unstable a...
The study was a retrospective review of ...
patients who presented as having Gro p 3 ...
unstable angina and who then showed ...
evidence of myocardial infarction over the first ...
hours in the coronary care unit. The med...
management was not standardized, about h...
the patients received anticoagulants—one th...
long acting nitrates and one sixth propran...
The incidence of myocardial infarction in hosp...
was very low, only 7 per cent. All but one of th...
myocardial infarctions occurred in the group of
patients who continued to experience prolo...
ischemic pain after 12 hours at bed rest. T...
hospital mortality rate was only 1 per cent, ...
single death occurring suddenly in an elderly m...
with a presumed infarct late in his hosp...
course The patients were followed after hosp...
discharge and during the first year a signific...
incidence of myocardial infarction and de...
appeared There were six further docume...
myocardial infarctions (two of whom died) se...
sudden deaths presumed secondary to myocard...
infarction, and three noncardiac deaths. Th...
the myocardial infarction rate after 1 year wa...
per cent and the mortality rate 15 per cent of
88 patients available for follow up

The study of Gazes and associates[31] is ...
interest because it is the first reported long te...
follow up study of unstable angina T...
prospectively followed for 10 years 140 patient...
whom they diagnosed preinfarction angina Gr...
2 or 3 prior to 1961 Patients were treated ...
bed rest, nitrates, sedatives, analgesia, low-c...
rie-low fat diets, and 91 of 140 were anticoag...
ted Beta blocking drugs were used only lat...
the follow up study At 3 months, acute myo...
dial infarction had developed in 20 7 per cent ...
death in 10 per cent They identified a subgr...
of 54 patients whose pain persisted after 48 ho...
of bed rest, among whom the 3 month myocar...
infarction rate was 35 per cent and the morta...
rate 26 per cent Of the total group, 18 per cen...
were dead at the end of 1 year whereas in th...
subgroup 43 per cent were dead The mortality
rates for the total group and the subgroup were
respectively, at 5 years 39 and 73 per cent, and a...
10 years 52 and 81 per cent Fifty one of 54
patients with persisting pain had had stable
angina prior to the diagnosis of preinfarction
angina

Several points emerge from these studies. First

is generally a significant reduction of
■

product of heart rate and blood pressure en used as an index of MVO_2 [18] and both are ı to rise in spontaneous attacks of angina [18] and associates [9] have studied 23 patients unstable angina (Group 3) whose mean rate rose from 75 to 90 beats per minute and blood pressure from 130/78 to 160/95 mm uring episodes of pain Twenty of these its received propranolol and in the 17 whose was abolished mean heart rate had fallen to ›m and mean systolic pressure to 113 mm n the three patients who did not respond the ı rate fell but the blood pressure remained ame or rose slightly Caution is warranted in patients in incipient congestive heart failure propranolol blockade of the compensatory sympathetic stimulation of the myocardium result in marked increases of left ventricular ne and the onset of frank congestive heart re [1] If the signs of congestive heart failure apparent only with pain as in seven of in s patients improvement of myocardial en balance with propranolol should resolve pain and the failure Digoxin and diuretics ıld supplement propranolol therapy if mild gestive heart failure is precipitated during the apy [9]

here is also some evidence that beta blockade lts in redirection of the limited blood supply n overperfused healthy areas to ischemic is.[3] Myocardial necrosis occurs when the alance between oxygen supply and demand omes critical and some myocardial cells can no ger remain viable The aim with propranolol is educe as much as possible the oxygen demand l possibly to redirect the supply for a time ficient for collaterals to develop or for redistri ıon of blood flow to occur so that myocardial crosis may be avoided

There are no controlled studies of the use of opranolol in unstable angina It has become a ndard component of therapy in many centers d it is now difficult to make conclusions about efficacy Five reports on propranolol therapy summarized in Table III Papazoglou[12] served seven patients with acute coronary sufficiency whom he treated with propranolol ter a mean 14 day period of intractable pain Six sponded rapidly with relief of pain with rather nall doses of propranolol (60 to 80 mg per day) and the seventh also had relief after several days when a dose of 160 mg per day was reached No follow up was provided Mizgala and associates[13] studied 15 patients with acute coronary insufficiency (Group 3) whose pain had persisted a mean of 14 7 days on medical therapy Patients were digitalized and given increasing doses of propranolol until symptoms subsided or until 400 mg per day was being given Thirteen out of 15 responded to an average dose of 220 mg per day There was no acute myocardial infarction or death among these 13 and during an average 64 7 week follow up the only event was sudden death in one patient The fate of the nonresponders is not reported

Fischl and associates [9] began propranolol therapy in 20 patients with intermediate coronary syndrome (Group 3) an average of 8 days after onset of pain The protocol involved initiation of therapy with 20 mg of oral propranolol The drug was then given every 4 hours and each successive dose was increased until pain was controlled or the heart rate remained consistently below 60 per minute during pain Seventeen of 20 patients experienced relief of pain and seven showed improvement of ischemic ECG changes within 12 hours Seven subjects with subsequent break through of pain were controlled by a further increase in propranolol dosage There were no acute myocardial infarctions or deaths The therapy was designed to stabilize the patients for angiography and subsequent surgery if indicated and accordingly 14 patients were operated upon Follow up of the nine medically maintained patients was carried out but the group is not comparable because in general the reason for not operating was extensive distal coronary artery disease

Conti and associates studied 50 patients with unstable angina pectoris (Group 3) who were angiographically suitable for aortocoronary by pass surgery Because of physician preference 10 of these were not operated upon but were main tained on anticoagulation nitrates and propran olol (average 160 mg per day) One patient suffered acute myocardial infarction and died in hospital. During the average 10 month follow up one further infarction occurred but was uncom plicated

Although these studies are uncontrolled there appears to be a consistent relief of the pain syndrome by propranolol, particularly well docu

Table III Propranolol therapy of unstable angina pectoris

Ref No	*Year*	*Name of syndrome*	*No of patients*	*Group*			*Dose of propranolol 24 hr (mg)*	*Acute*			*Follow-up*
				I	*II*	*III*		*Pain relief*	*MI*	*Death*	
42	1971	Acute coronary insufficiency	7		7		60 160	100% (7/7)	0	0	
43	1969	Acute coronary insufficiency	15			15	160 400 (Avg 220)	87% (13/15)	0	0	Avg 15 mo 7% (1 1 mortality rate
40	1973	Intermediate coronary syndrome	20			20	40-400 (Avg 170)	85% (17/20)	0	0	
[illegible]	1973	Unstable angina	10	10			(Avg 160)		10% (1/10)	10% (1/10)	Avg. 10 mo 10% (1 10 pain free 50% (5) improved I none fatal
58	1974	Impending infarction	18	18			30 320 (Avg 160)	100% (18/18)	28% (5/18) subendocardial	0	

trol' patients The last 30 patients to enter the control" group did so because anticoagulants were deemed undesirable for a variety of reasons The therapeutic regimens appeared to differ only with regard to anticoagulation suggesting that anticoagulation was justified in unstable angina The faults with the sampling procedure may have introduced a bias which could invalidate this conclusion, however

Vakil[27] reported an anticoagulant trial of 360 patients with 'preinfarction syndrome (Group 3) treated between 1949 and 1963 All patients were put at bed rest and sedated The anticoagulated group (190 patients) and the control group (156 patients) were said to be well matched but the treatment allocation procedure was not specified Within 3 months of diagnosis, acute myocardial infarction had occurred in 36 3 per cent of the anticoagulated patients (mortality rate 9 5 per cent) and in 49 4 per cent of the control patients (mortality rate 23 7 per cent) Vakil concluded that a statistically significant reduction in acute myocardial infarction and particularly in mortality rate was evident in the anticoagulated group This conclusion may not be justified when one considers the deficiencies in study design, particularly in relation to treatment allocation

Nichol and associates[33] reported a 30 day infarction rate of 6 6 per cent with 1 6 per cent mortality rate in 318 patients treated with coagulants There was no control group howe and the criteria of infarction were inadequate present standards

The belief, now questioned,[22 35 34] that coro ry thrombosis preceded myocardial infarct encouraged the enthusiastic investigation of coagulant therapy of the 'preinfarction drome The impression emerged that anticoagu tion of patients with unstable angina was bene cial However, there is in fact no well design and properly controlled study available fr which a judgment can be made

Beta adrenergic blockade Propranolol h become established as an effective drug for t amelioration of stable angina pectoris[36] The dr blocks beta sympathetic stimulation of the hea and great vessels resulting in a net reduction myocardial oxygen consumption (MVo_2) for given level of body demand for cardiac output The determinants of MVo_2 are several, the m important ones being contractile state of heart heart rate, and wall tension (proportio to blood pressure and ventricular radius) plu duration of contraction and others of importance[37] Propranolol reduces contractilit and heart rate but in turn prolongs systolic ejection time and tends to increase wall tension by increasing ventricular volume[36] In patients without congestive heart failure however, the ne

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Follow up of the nine medically maintained
patients was carried out but the group is not
comparable because in general the reason for not
operating was extensive distal coronary artery
disease

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Table IV Surgical management of unstable angina pectoris

Ref No	Year	Name of syndrome	Avg age	No of patients	Group I	Group II	Group III	Angiography	In
56	1972	Preinfarction angina		80		80			
57	1972	Unstable angina		98					
		a Crescendo angina				64 25 early surgery 39 1 mo surgery			
		b Acute coronary insufficiency					34		
6	1973	Unstable angina		40		40		2 deaths 1 AMI	19
50	1973	Preinfarction angina	51	67			67 59 uncomplicated 8 complicated		15
53	1973	Impending infarction	56	63			63	6 AMI but then removed from study	97
52	1973	Accelerated angina pectoris	53	48		48		2 AMI	29
61	1974	Unstable angina	53 3	97 surgery 57			39 no preop AMI		19
		a Progressive angina				33			
		b Intermediate syndrome					24		
				medical 40					12 5
		a Progressive angina			20				
		b Intermediate syndrome					20		

mented in the study of Fischl and associates The incidence of acute myocardial infarction and early death is low in the recent reports of medically managed patients with unstable angina—but these incidence rates are even lower in the propranolol treatment series The hazards of drawing conclusions from uncontrolled studies are well known, and a controlled study of propranolol in unstable angina would be highly desirable

Revascularization The medical therapy unstable angina does not resolve the ba problem of inadequate coronary blood flow to region The anatomic characterization of athe sclerotic coronary artery disease by selecti coronary angiography has made reconstruct

In hospital		Follow-up						
					Acute MI		Death	
Death	Death of stable angina elective surgery in same center	Avg time (mo)	Symptoms	Graft patency	Further	Total	Further	Total
2.5% (?/80)		12	92 5% (74/80) Improved				2/78	5% (4/80)
28% (7/25)								
5% (2/39)								
0								
22% (9/40)	3 4%	16 7	5% (30/40) marked improvement 52.5% (21/40) pain free	56% (14/25 grafts studied)	1/31		0	22% (9/40)
10 4% (7/67)	1 5%	6 8	?8% (52/67) significant improvement 70% (47/67) angina free	?5% (18/24 grafts studied)	6/60	18% (12/67)	2/60	13% (9/67)
8 5% (5/59)								
25% (2/8)								
6.4% (4/63)	4 0%[10]		87% (55/63) symptom free	92.3% (36/39 grafts studied)				
12.5% (6/48)			5% (36/48) improved 50% (24/48) pain free					
10% (4/39)								
7% (4/57)		8.3					0	7% (4/57)
6% (2/33)								6% (2/33)
8 5% (2/24)								8.5% (2/24)
1 % (6/40)		8 3					2/34	20% (8/40)
								35% (7/20)
								5% (1/20)

rgery possible The desirability of attempting ich surgery in patients with unstable angina was nmediately apparent With internal mammary rtery implantation months are required for ollaterals to develop However saphenous vein ortocoronary bypass grafting[4] and internal nammary artery to coronary artery anastomo is[5] result in an immediate increase in flow These techniques might be expected to correct the critical imbalance of oxygen supply and demand in unstable angina relieving pain and preventing myocardial infarction and death

The enthusiasm for emergency bypass graft surgery has stemmed from encouraging early reports on small numbers of patients [6-9] How ever to evaluate this form of therapy one must

Table V Relationship between extent of coronary artery disease and operative deaths in patients with unstable angina pectoris

Ref No	*Patients with 3 vessel disease (%)*	*Operative death (%)*
6	56	22
52	47	12.5
50	39	10.4
51	42	7
[illegible]	32	6.4

examine larger series with adequately defined patient populations. The need for emergency surgery is based upon the belief that the incidence of myocardial infarction and death can be reduced, and therefore these are the parameters to be examined in these series and to be compared to the series of medically treated patients Improvement of symptoms by revascularization surgery is desirable, but to justify emergency procedures, a reduction of myocardial infarction and early death must be demonstrated

A potential source of morbidity and death which must be considered is that occurring during coronary angiography Some investigators have found that coronary angiography can be done on patients with unstable angina at a risk not greater than that for patients with stable angina[50, 51] but there is a clear increased risk during coronary angiography in some reports Thus in one series[6] of 57 patients two died and one sustained nonfatal myocardial infarction in another[52] two of 79 patients suffered nonfatal myocardial infarction, in a third[53] six of 69 patients sustained nonfatal myocardial infarction (although these six were then removed from the unstable angina group) These patients are of course at moderate risk of developing acute myocardial infarction spontaneously and therefore it is difficult to assess the role of angiography in precipitating acute myocardial infarction There is clearly some increased risk of angiography over those patients with stable angina

The results of several large studies of saphenous vein bypass graft surgery for unstable angina are presented in Table IV It is evident that most groups do not operate upon patients in Group 1 The only adequately controlled study is that of Bertolasi and associates,[51] in which 97 patients with Group 2 or Group 3 unstable angina underwent coronary angiography and randomized to medical or surgical T surgical mortality rate was 7 per cent, the acute medical mortality rate was 1 The myocardial infarction rate was for either group There was a history infarction in 40 per cent of the surgical and in 55 per cent of the medical patients. T authors concluded that there was a sig reduction of mortality rate in Group 3 (diate syndrome ') from 35 per cent w therapy to 8 5 per cent with surgical could show no significant difference in Group ('progressive angina '), where respective ty rates were 5 and 8 per cent. F extended to only 8 3 months, during which there were no further deaths in the surgical group two deaths in the medical group

The study of Conti and group of 10 patients who were angiographically suited to surgery but whose physicians refused The hospital mortality rate of these medically managed patients was 10 per cent. The hospital mortality rate of the surgically managed patients was 22 per cent. The surgical patients did be in late follow up, with 75 per cent showing marked improvement in symptoms, 53 per cent pain free and one patient developing acute myocardial infarction after 6 months. Of the medical patients, 60 per cent were symptomatically improved and one developed myocardial infarction in 6 months.

The Cleveland Clinic has had the largest experience with aortocoronary bypass surgery of any center Cheanvechai and associates[53] reported 63 patients operated upon for Group 3 unstable angina with a postoperative mortality rate of 6.4 per cent and myocardial infarction rate of 14 per cent (presuming three of the four deaths to be the result of myocardial infarction) The patients did well during an unspecified follow up 79 per cent being pain free and 6 per cent continuing to have angina Coronary angiography was repeated in 20 patients with 39 grafts 6 weeks to 1 year postoperatively revealing an over all patency rate of 92.3 per cent of grafts studied

An important surgical risk factor is the presence of severe left ventricular dysfunction diagnosed by the presence of clinical congestive heart failure and by angiographic parameters.[54, 55] Surgical risk also increases with the number of vessels significantly stenosed.[6, 50, 53] In the series of

and associates[4] all six postoperative deaths ed in patients with triple vessel disease Scanlon and associates[32] found a high lity rate in patients with more than three disease An interesting table (Table V) may nstructed relating operative death to the t of coronary artery disease and may lly explain the wide variation in operative ality rates among the reporting centres the 22 per cent mortality rate in the study nti and associates occurred in a series of 57 1 per cent had triple vessel disease eas by contrast the 6 4 per cent mortality in the study of Cheanvechai and associates rred in a series of whom only 31 per cent had vessel disease A history of previous cardial infarction was not found to be of nostic significance by Miller[5] or Scanlon[32] associates Bertolasi and associates[31] how showed a correlation between previous cardial infarction and diminished left ven ilar function (a well known relationship in le angina) and their ongoing study is designed eveal differences in operative mortality rates ween patients with and without previous ocardial infarction once enough patients have n studied. Left ventricular dysfunction extent oronary artery disease and history of myocar l infarction are interrelated and would be pected to be risk factors in bypass surgery

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Comparisons between medical and surgical series are further confounded by the practice of omitting from a surgical series those patients who have infarction before surgery On the other hand, the tendency to operate only on those patients who are doing less well in terms of relief of pain by medical therapy results in the selection of higher risk patients for surgical as opposed to medical therapy Until adequate control series are available authors reporting surgical results must resist a tendency to use for comparison groups those patients not operated on in the particular study being reported or those medi cally treated patients reported in the literature of the early 1960 s The first group is invariably a highly selected group of patients many of whom could not be operated upon and no comparison should even be implied The latter comparison is clearly not valid since the current early outcome in unstable angina is vastly better than that reported in the early studies

A number of observations can be made about angiography and aortocoronary bypass surgery in unstable angina. The risk of coronary angio graphy varies from center to center but it is clearly higher than the risk in stable angina Operative mortality rates again vary ranging from 2 5 to 22 per cent but in every center reporting the rate is distinctly higher in unstable angina than in stable angina operated upon elec tively in the same institution [30, 33] The incidence of myocardial infarction related to operation is significant when looked for (up to 25 per cent[32]) and is the major cause of death Death is related to left ventricular dysfunction to extent of coronary artery disease and possibly to the history of previous myocardial infarction The early (up to 1 year) follow up of these patients is highly favorable with complete relief of symp toms in 50 to 87 per cent improvement in 75 to 93 per cent and a low incidence of further deaths Graft patency is clearly less than in elective surgical procedures and ranges from 56 to 92 3 per cent of grafts studied

In the absence of definitive data a pattern of management of unstable angina has developed whereby most centers hospitalize and put at bed rest patients in Groups 2 or 3 Group 1 patients are generally considered less at risk and are managed by reduction of activities Pain is controlled by analgesics if necessary but an attempt is made to alter the myocardial oxygen supply demand imbalance with nitrates and propranolol Although the available studies of anticoagulants support their use there is a decreasing tendency to employ them There has been a major trend to angiography and aortocor

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Summary

Unstable angina is a syndrome which comprises a spectrum of symptomatic manifestations of coronary artery disease which lies between stable angina pectoris and acute myocardial infarction Patients fall into three groups angina of recent onset (4 weeks) angina of changing pattern, and angina occurring at rest (longer than 15 minutes) The syndrome may presage acute myocardial infarction or sudden death, or may itself be the manifestation of a myocardial infarction The pathophysiology may involve primary cardiac events or extracardiac precipitating factors and does not appear to be the consequence of a particular anatomic pattern of coronary artery disease Pain may occur as a result of regional reduction of coronary flow to pressure dependent areas of myocardium during states of increased myocardial oxygen demand Persisting ischemia leads to infarction via a series of events which may include myocardial edema formation, increased beta sympathetic tone and others which have been experimentally modified by interventions designed to limit infarct size

Although the incidence of acute myocardial infarction and death was high in early reports, in recent reports acute infarction occurs in 15 5 per cent and death in under 2 per cent Patients at high risk are those whose with bed rest, and those with preceding angina pectoris or myocardial infarction Prognostic differences among Groups 1 2, and 3 exist but cannot be assessed from available series

Studies of the management of unstable have generally been uncontrolled tion, bed rest, and short are generally employed in Groups 2 and and the marked reduction in myocardial infarction rates from early to recent studies support these approaches *Anticoagulants* less used now than formerly *Propranolol* produce a significant reduction of oxygen consumption and may redirect flow to ischemic areas The drug has effectively controlled pain in several studies and is widely used to manage unstable angina *coronary bypass surgery* has been extensively employed but there is only one preliminary of a controlled study available The role surgery is not yet defined The optimal approach to therapy may eventually involve the use medical therapy, including beta blockade stabilize patients, with delayed semielective coronary angiography and surgery in those who respond Emergency angiography and surgery might then be reserved for the high risk group patients whose pain persists during optimal medical therapy

REFERENCES

1 Resnick W H Preinfarction angina I The transaminase test—A diagnostic aid Mod Concepts Cardiovasc Dis 31 751 1962
2 Master A M Dack S Grishman A Field L E and Horn H Acute coronary insufficiency An entity shock hemorrhage and pulmonary embolism as factors in its production J Mt Sinai Hosp 14 8 1947
3 Graybiel, A The intermediate coronary syndrome US Armed Forces Med J 6 1 1955
4 Fowler N O Angina pectoris Clinical diagnosis, Circulation 46 1079 1972
5 Fowler N O Preinfarctional angina C 44 755 1971
6 Conti C R Brawley R K Griffith L S C, Pitt, B, Humphries, J O Gott, V and Ross, R Unstable

...ina pectoris Morbidity and mortality in 57 consecutive patients evaluated angiographically Am J Cardiol ... 45 1973
...lton, M Lutz W., Donald K W Kirby B J., ...ncan B Morrison S L Kerr F and Julian D G ...tural history of unstable angina Lancet 1 860 1972
...mstrong, A. Duncan B., Oliver M F., Julian D G ...onald K.W Fulton M., Lutz W and Morrison S L. ...tural history of acute coronary heart attacks. A ...mmunity study Br Heart J 34 67 1972
...annon, D A., Harrison D C and Schroeder J S ...aemodynamic observations in patients with unstable ...igina pectoris, Am J Cardiol 33 1 1974
...asen, A Pathophysiology coronary spasm and Prinz...etal angina, in Proceedings of VII International ...ongress of Cardiology Buenos Aires, Argentina ...eptember 1974
...rinzmetal, M Kennamur R. Merliss, R Wado T ...nd Bor N Angina pectoris. I A variant form of angina ...ectoris Preliminary report Am J Med 26 375 1959
...orlin, R. Pathophysiology of cardiac pain Circulation ...2 138, 1965
...Becker J Lichtlen P., Baumann P C Preter H ...lbert, H Kaltenbach, M Kober G Kollath J and ...pitz P History and clinical findings related to selective coronary angiography in Kaltenbach, M., and Lichtlen P editors Coronary artery disease Stuttgart 1971 Georg Thieme Verlag, p 56
...Masen, A. Methods of studying regional myocardial flow and alterations during angina in Oliver M F Julian, D G and Donald K W editors Effect of acute ischaemia on myocardial function Edinburgh 1972, Churchill Livingstone p 56
Klassen, G A., and Tanser P H Effect of atrial pacing on total flow and volume of the diseased left coronary artery Clin Res. 19 323 1971
Klassen G A Agarwal, J B., Tanser P H Woodhouse S P and Marpole D G F Blood flow and tissue space of the left coronary artery in man Circ Res 27 185 1970
Leaf, A. Cell swelling A factor in ischaemic tissue injury Circulation 48 455 1973
Willerson J T Powell, W J Guiney T E Stark J J Sanders C A., and Leaf A Improvement in myocardial function and coronary blood flow in ischaemic myocardium after mannitol, J Clin Invest. 51 2989 1972
Fitzgerald J D The role of beta adrenergic blockade in acute myocardial ischaemia in Oliver M F Julian D G and Donald, K. W editors Effect of acute myocardial ischaemia on myocardial function Edinburgh 1972 Churchill Livingstone p 521
Shell, W E Lavelle J F Covell, J W., and Sobel, B E Early estimation of myocardial damage in conscious dogs and patients with evolving acute myocardial infarction J Clin Invest. 52 25 9 1973
Maroko P E and Braunwald E Modification of myocardial infarction size Ann. Intern. Med 79 720 1973
Roberts W C and Buja L M The frequency and significance of coronary arterial thrombi and other observations in fatal acute myocardial infarction Am. J Med. 52 425 1972
Levy H The natural history of changing patterns of angina pectoris, Ann Intern Med. 44 1123 1956.
Beamish, R. E and Storrie V M Impending myocardial infarction Recognition and management Circulation 21 1107 1960
Wood, P Acute and subacute coronary insufficiency Br Med. J 1 1179 1961

26 Vakil R. J., Intermediate coronary syndrome, Circulation 24 557 1961
27 Vakil R J Preinfarction syndrome—management and follow up Am J Cardiol. 14 55 1964
28 Gazes P C Mobley E. M Jr., Faris H M Jr., Duncan R C and Humphries, G B Preinfarctional (unstable) angina—a prospective study—ten year follow up Prognostic significance of electrocardiographic changes, Circulation 48 331 1973
29 Watkins P C Russell, R. O., Jr and Rackley C E Follow up study of unstable angina in a myocardial infarction research unit (abst) Circulation 46 (Suppl. II) II 23 1972
30 Krauss, K R Hutter A M., Jr and Desanctis, R W Acute coronary insufficiency course and follow up Circulation 45 (Suppl I) I 66 1972.
31 Gifford R. H and Feinstein A R A critique of methodology in studies of anticoagulant therapy for acute myocardial infarction N Engl J Med 280 351 1969
32 Editorial Long term anticoagulants after acute myocardial infarction Lancet 1 226, 1970
33 Nichol, E S., Phillips, W C and Casten G G Virtue of prompt anticoagulant therapy in impending myocardial infarction Experiences with 318 patients during a 10-year period, Ann Intern Med. 50 1158 1959
34 Chapman I The cause-effect relationship between recent coronary artery occlusion and acute myocardial infarction Am. Heart J 87 267 1974
35 Roberts W C Coronary thrombosis and fatal myocardial ischaemia Circulation 49 1 1974
36 Epstein, S E Redwood D R Goldstein R E., Beiser G D Rosing, D R., Glancy D L., Reis R L and Stinson E B Angina pectoris Pathophysiology evaluation and treatment Ann Intern Med 75 263 1971
37 Braunwald, E Control of myocardial oxygen consumption Physiologic and clinical considerations, Am. J Cardiol. 27 416 1971
38 Watson S and Gorlin R Cardiovascular pharmacology of propranolol in man Circulation 40 401 1969
39 Robinson B F Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris, Circulation 35 1073 1967
40 Fischl, S J., Herman, M V., and Gorlin R The intermediate coronary syndrome Clinical angiographic and therapeutic aspects N Engl. J Med 288 1193 1973
41 Fitzgerald, J D Perspectives in adrenergic beta receptor blockade Clin Pharmacol. Ther 10 292 1969
42 Papazoglov N M Use of propranolol in preinfarction angina Circulation 44 303 1971
43 Mizgala H F Khan A. S., and Davies, R O The effect of propranolol in acute coronary insufficiency A preliminary report (abst) Clin Res. 17 637 1969
44 Effler D B Current era of revascularization surgery Surg. Clin North Am. 51 1009 1971
45 Green G E Internal mammary artery to-coronary artery anastomosis, Ann Thorac Surg 14 260 1972
46 Hill, J D Kerth, W J Kelly J J Selzer A., Armstrong W Popper R W., Langston M F and Cohn K E Emergency aorto-coronary bypass for impending or extending myocardial infarction Circulation 43 (Suppl. I) I 105 1971
47 Pifarre R Spinazzola A., Nemickas, R Scanlon P J., and Rohin J R Emergency aorto-coronary bypass for acute myocardial infarction Arch Surg 103 525 1971
48 Favaloro R. G., Effler D G Cheanvechai, C., Quint R A and Sones F M., Jr Acute coronary insufficiency (impending myocardial infarction and myocardial infarc

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iac trauma

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natic injuries constitute one of the leading of morbidity and death in our society[1] A r cause for this morbidity and death is a to the heart During recent years with increase in traffic accidents and social ence there has been a parallel rise of cardiac y from both nonpenetrating and penetrating na

npenetrating trauma to the heart may cause ricardial rupture (2) myocardial contusion upture of the free cardiac wall interventri septum aortic valve atrioventricular s chordae tendineae or papillary muscles (4) injury to the coronary arteries[2] Pene ng cardiac injury will cause damage to the e anatomical structure Diagnosis and treat t of penetrating and nonpenetrating injuries vary and will be discussed later

ontusion of the heart

n 1676 Oloff Borch[3] reported the case of an 8 r old boy who was felt to have cardiac contu n following severe blunt trauma to the chest 1859 Schnabel described a man who died eral hours after a nonpenetrating chest injury l at autopsy in addition to other injuries had ltiple sites of epicardial hemorrhages Numer s reports of cardiac contusion followed these tial descriptions but no accurate statistics ncerning the incidence of cardiac injury lowing blunt chest trauma were reported[4] ntusion of the heart was initially thought to be frequent With increasing physician awareness d increasing severity of blunt chest trauma wever it became clear that such injuries did cur in significant numbers. Autopsy studies in unselected auto accident victims have shown myocardial contusion in 15 to 17 per cent and in severe body trauma there was an incidence of 76 per cent[5]

The etiology of cardiac contusion may vary from a simple blow from a fist to the steering wheel injury The latter is the most common cause of blunt trauma to the heart

The heart which hangs freely in the chest cavity between the sternum and thoracic verte bra is suspended from above by the great vessels As such it is subject to trauma by a number of mechanisms[6, 11, 5] (1) sudden accelerations or decelerations may cause the heart to be thrust against the sternum or vertebra injuring the myocardium (2) the heart may be compressed between the sternum and vertebra if the sternum is suddenly driven in by a forceful blow (steering wheel injury) (3) sudden increase in intratho racic or intra abdominal pressure may result in cardiac injury with subendocardial hemorrhage or rupture of the heart[7, 19] All of these injuries may occur without actual fractures of the bony structures of the chest wall[19, 6]

Pathologic changes The pathologic lesions in myocardial contusion can be small areas of pete chiae or ecchymosis in the subendocordium or subepicardium full thickness contusion of the myocardial wall or rupture of the heart Micro scopic examination of an acute myocardial contu sion will reveal numerous red blood cells in the interspaces between myocardial fibers The mus cle fibers themselves will be edematous frag mented and often necrotic Later polymorpho nuclear leukocytes will infiltrate the area of hemorrhage and the muscle fibers will appear swollen have lumpy cytoplasm and have partial loss of tranverse striations[9, 21] In survivors the areas of damaged myocardium undergoes soften ing infiltration of inflammatory cells and even tual healing by scar formation[22] Full thickness myocardial contusions will then be subject to the

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eprint requests. Dr N Symbas, 69 B tler Street, S E Atlanta a. 30303.

tion) Surgical treatment by the saphenous vein graft technique Am J Cardiol 28 598, 1971

49 Lambert, C J Adam M Geisler G F Verzosa E Nazarian M and Mitchel, B F Jr Emergency myocardial revascularization for impending infarctions and arrhythmias J Thorac Cardiovasc Surg 62 522 1971

50 Miller D C Cannom D S Fogarty T J Schroeder J S Daily P O and Harrison D C Saphenous vein coronary artery bypass in patients with "preinfarction angina Circulation 47 234 1973

51 Bertolasi C A Tronge J E Carreno C A Jalon J and Vega M R Unstable angina—prospective and randomized study of its evolution with and without surgery Preliminary report Am J Cardiol 33 201 1974

52 Scanlon P J Nemickas R Moran J F Talano J V Amirparviz F and Pifarre R Accelerated angina pectoris. Clinical hemodynamic arteriographic and therapeutic experience in 85 patients Circulation 47 19 1973

53 Cheanvechai, C Effler D B Loop F D Groves L K Sheldon W C Razavi M and Sones F M Jr Emergency myocardial revascularization Am [illegible] 32 901 1973

54 Gott V L. Outlook for patients after coronary revascularization Am J Cardiol. 33 431 1974

55 Dawson J T., Hall R J Hallman, G L. and [illegible] D A Mortality in patients undergoing coronary bypass surgery after myocardial infarction, [illegible] Cardiol 33 483 1974

56 Flemma R J Johnson W D Tector A J [illegible] D Jr , and Blitz J Surgical treatment for preinfarction angina Arch. Intern Med. 129 828, 1972

57 Theroux P and Campeau L. Aorto-coronary surgery for unstable angina (abst.) [illegible] (Suppl II) II 229 1972

58 Master A M and Jaffe H L. Propranolol [illegible] nous vein graft bypass for impending infarction [illegible] farction syndrome) AM HEART J 87 371 [illegible]

59 Sheldon W C Rincon G Effler D B Proudfit [illegible] and Sones F M., Jr Vein graft surgery for coronary artery disease Survival and angiographic results [illegible] the first one thousand patients (abst.) Circulation [illegible] (Suppl II) II 110 1972

…l rest and early recognition and treatment of …ythmias is paramount Anticoagulants are …avoided as they may precipitate intramyo…al or intrapericardial hemorrhage Oxygen …d be administered if hypoxemia is present …alis is of value in cardiac failure or atrial …lation with rapid ventricular response …ugh reversion to sinus rhythm with bed rest … is the rule Digitalis is ineffective in sinus …ycardia and may accentuate the electrical …bility of contused ventricular myocardium …caine procaine and quinidine may be useful …ontrol of ectopic beats or tachyarrhythmias …nary vasodilators have virtually no effect on … *which is best treated with narcotics*

…he prognosis of patients with myocardial …usion for partial or complete recovery is good …sequelae vary from no cardiac disability to …h from complications particularly ventric… dysrhythmias or cardiac rupture Clinical …rovement and reversion of the ECG to normal *…ally occurs within a month although this is* …iable [14 … 9]

Rupture of the heart

…orceful compression against the vertebral …umn may cause rupture of the heart at the …ne of injury Immediate myocardial discon…uity may also be caused by laceration from a …arp rib or sternal bone fragment or delayed …pture may occur at the site of a myocardial …ntusion as late as 2 weeks following the initial …unt trauma [33] Very rarely the heart may be …ptured by violent compression applied to the …domen and legs The cardiac rupture may *…olve the free wall* … with clinical mani…stations of hemopericardium and cardiac tam…onade or may involve the interventricular …ptum … or the aortic … mitral … or tricus…id valves with symptoms and signs of inter…entricular shunt valvular regurgitation and …ongestive heart failure

… *The diagnosis* of rupture of the heart should be …uspected when a patient experiences severe blunt …njury and has a clinical picture of cardiac …amponade or congestive heart failure In the face …of symptoms and signs of cardiac tamponade …however massive myocardial contusion must be …considered as the clinical manifestations may be …identical to *those of cardiac* rupture In such …cases pericardiocentesis should be performed immediately to relieve possible cardiac tamponade but the diagnosis *should be confirmed at* emergency thoracotomy and followed by closure of the cardiac defect [4]

The diagnosis of rupture of the cardiac valves or interventricular septum should be suspected in patients who sustain severe blunt trauma and develop congestive heart failure The symptoms of cardiac decompensation in these patients may appear immediately after the injury or following a relatively asymptomatic period of days or even years The diagnosis of rupture of the cardiac valves or ventricular septum should be strongly suspected in patients who develop a valvular regurgitant murmur or murmur of ventricular septal defect (with or without symptoms of cardiac decompensation) following severe blunt trauma

In the symptomatic patient with rupture of the cardiac valves or interventricular septum the treatment should be supportive before and after *the diagnosis is established Common measures* used include assisted ventilation good pulmonary toilet and careful administration of digitalis and diuretics If the patient fails to respond to this treatment cardiac catheterization should be performed as soon as possible Clinical deteriora tion combined with the specific data of cardiac *catheterization* will serve as indicators for emer gency surgical repair … In patients with compensated congestive heart failure cardiac catheterization and angiography should be per formed following recovery from the initial trauma If the cardiac lesion is found to be hemodynamically *significant elective repair* should then be performed …

C Penetrating wounds of the heart

The grave prognosis of *penetrating cardiac* wounds has been recognized since antiquity Hippocrates realized their fatal nature … and all wounds of the heart were said to be mortal by Boerhaave[40] in 1709 In 1896 Paget wrote Sur gery of the heart has probably reached the limits set by nature to all surgery no new method and no new discovery *can overcome* the natural diffi culties that attend a wound to the heart In the later part of the 18th century however the observation of scars on the hearts of individuals who had been known to have precordial wounds caused some to question the current teachings

same complication as myocardial infarction, i e , rupture of the softened area or myocardial failure with or without aneurysm formation [19, 3, 26]

Clinical manifestations Functional disturbances will not always reflect the severity of anatomic damage in the heart and fatal dysrhythmias can be produced experimentally without demonstrable pathologic changes,[8, 21] but the clinical picture of myocardial contusion usually does depend, to a degree, upon the extent and type of lesion Most injuries probably produce no significant dysfunction and go unrecognized, others are overlooked because of concomitant injuries to other organs

The most common symptom of myocardial contusion is pain which in character location, and radiation is identical to the pain of myocardial ischemia[13, 19, 1] and is usually unaffected by coronary vasodilators[14] Asymptomatic myocardial contusions may occur[3] but it may be that a typical description of pain is not obtained because a detailed history is not available or because of more severe pain from other injuries With severe contusions, dyspnea and hypotension may be present Cardiac failure[27, 8] however is rare and electrical instability[1, 6, 9] more common Auscultation may disclose the rub of pericarditis as well as various murmurs which result from dysfunction of injured myocardium, papillary muscles, chordae tendineae or valves

The majority of patients with traumatic heart disease have symptoms immediately, but these may be delayed for an hour or days The most common late symptoms are congestive heart failure or pain similar to angina pectoris brought on by exertion Palpations and tachycardia are frequent features, with premature atrial or ventricular contractions being the most common rhythm disturbance Virtually all dysrhythmias have been produced experimentally or have been seen in patients with myocardial contusion Atrial fibrillation flutter sinoatrial block nodal rhythm, atrioventricular block and idioventricular rhythm have also been observed[12, 3, 6, 8, 9, 30, 36] Paroxysmal atrial tachycardia is uncommon but paroxysmal ventricular tachycardia, fibrillation, and idioventricular rhythm are frequent causes of death[13]

It should be emphasized that myocardial contusion may often be overshadowed by the more overt manifestations of cerebral, abdominal or musculoskeletal injuries frequently pre- the multiple trauma victim unless this i- considered and sought out

Diagnosis Presently the most readily a- diagnostic test for myocardial contusion is- lead electrocardiogram (ECG) which sh- obtained in all patients who sustain blunt - to the chest, particularly involving the p- dium ECG abnormalities that are precipita- contusion of the heart range from tra- long lasting disturbances of rhythm to - of pericarditis or focal muscular dam- changes typical of myocardial infarction T- abnormalities, which may return to normal much shorter time than those produced by - myocardial infarction, are frequently p- shortly after the trauma, but may not a- until 24 to 48 hours later Therefore, serial EC- should be done in patients who sustain - trauma to the thorax to detect the early - late appearing ECG changes Unfortuna- ECG abnormalities other than those indica- muscle damage from cardiac contusion are tively nonspecific since they can be preci- by other conditions not infrequently prese- traumatized patient (hypoxia hypovol- shock etc) Despite the error in specificity repeated 12 lead ECG s have proved to be most reliable diagnostic tool in accurately - ating patients with suspected cardiac contu- Other laboratory studies have not been found be of great diagnostic value[10, 11] Serum enz- are frequently elevated in liver lung and le- muscle injuries or in hemorrhagic shock and - not very useful in establishing this diag- sis[3, 1, 4]

Coronary arteriography late after contu- has not been diagnostic[30] Angiographic stud- fresh autopsy specimens of contused hea- however have shown extravasation in the area the contusion[4, 41] The use of radioisotopes - diagnose myocardial contusion is under inve- tion Coronary injection of technicium albu- microspheres demonstrates cold' areas in expe- mental myocardial contusion[44, 3] Positive im- ing of myocardial contusion using technic- tagged phosphatic compounds appears prom- to date

Treatment The treatment of myocardi- contusion like that of myocardial infarction expectant and symptomatic A 2 to 4 week peri-

cted in the presence of a penetrating wound chest neck upper abdomen or particularly precordium or if a missile traverses the astinum The majority of patients with pene ng cardiac wounds (81 [94 97] or 60 per [9 0 0]) succumb shortly after injury from iac tamponade or massive bleeding Most of remaining patients present with symptoms signs of cardiac tamponade or hypotension hemothorax Rarely such patients will ent with only evidence of elevated central ous pressure In patients presenting with othorax and continuous bleeding the diag s of penetrating cardiac injury is made at acotomy

gitation lack of cooperation air hunger cool clammy skin neck vein distension Kuss il s sign paradoxical pulse muffled heart nds and elevated central venous pressure in ients with penetrating wounds of the precor m neck chest and upper abdomen strongly gest penetrating injury to the heart with nponade Although with these clinical find s cardiac tamponade is relatively easy to gnose it may not be so in certain clinical tings When ethanol intoxication for example present it may produce many of the signs of mponade particularly the neurological mani tations Such patients should be thoroughly amined and pericardial tamponade excluded fore the agitation and the lack of cooperation are attributed to the intoxication In patients th hemothorax and pericardial tamponade the inical picture may be attributed to just blood ss when volume expansion markedly improves e hemodynamic parameters In such patients owever cardiac tamponade should be strongly aspected and searched for since volume expan on which increases the filling pressure will esult in clinical improvement of patients with emothorax and tamponade or tamponade lone [90] Neck vein distension and/or a central enous pressure of 12 cm saline or greater in such nstances strongly suggest pericardial tamponade ather than hypotension due to blood loss lthough these signs may be misleading particu arly when other conditions which may produce levation of the central venous pressure are pres ent

Roentgenographic studies are of limited value for the diagnosis of penetrating wounds of the heart

Fluoroscopy of the chest showing decreased cardiac motion is of slight value in diagnosing acute traumatic pericardial tamponade and chest roentgenography which has almost no value in the diagnosis of acute traumatic pericardial tamponade should be utilized only for diagnosing injury to other organs Either of these procedures may be performed only under close observation and in stable patients in whom the diagnosis is suspected

Treatment Thus when signs of pericardial tamponade are present in a patient with an external wound that might result in cardiac perforation pericardiocentesis should be per formed at once If nonclotting blood is obtained the diagnosis is established and the decompres sion of the pericardial sac provides the initial effective treatment of the injury

The pericardiocentesis is done with a thin walled metal needle or preferably a plastic number 17 or number 18 gauge catheter or needle through the left substernal paraxyphoid route with the patient in a semierect position of 35 to 40 degrees and with the needle pointing toward the left shoulder When a metal needle is used the pericardiocentesis should be preferably done under constant ECG monitoring Although the ECG is helpful in indicating when the pericardio centesis needle is in contact with the myocar dium [92] it should be used only when its use does not force an undue delay in performance of pericardiocentesis If a plastic catheter or needle is used for the pericardiocentesis it should be left in place for continuous drainage of the intraperi cardial blood until the cardiac wound is surgically repaired

Because vigorous and rapid resuscitation is often necessary for patients with penetrating cardiac wound this should be undertaken when ever possible by more than one physician Routes should be established for administering blood or fluid a central venous catheter should be placed and pericardiocentesis and evacuation of blood from the pleural space should be accomplished rapidly

The definitive treatment for patients with cardiac wounds and massive unrelenting blood loss is exploratory thoracotomy and cardiorrha phy The definitive treatment for the patients with cardiac wounds and cardiac tamponade however has not been uniform After the historic introduction of cardiorrhaphy for cardiac wounds

and in 1882 Bloch[a] sutured the hearts of rabbits and in 1895 deVecchio[a] successfully repaired stab wounds in the hearts of dogs This led to the first successful cardiorrhaphy in man, performed by Rehn[94] in 1896

Treatment of cardiac wounds by aspiration of the pericardial sac was suggested as early as 1649 by Riolanus[a] Pericardial decompression for a penetrating cardiac wound was attempted in 1826 when the French duc de Berry was stabbed in the heart by an assassin Dupuytren,[96] his surgeon, kept him alive for several hours by introducing a probe into the wound thus presumably relieving his cardiac tamponade In 1829 Larrey decompressed a wounded heart by aspiration and demonstrated that in dogs, cardiac injuries were not necessarily fatal

These early contributions and those of others growing out of experience received during the world wars in the management of cardiac wounds has refuted the earlier pessimism of Paget and others and has permitted realization of reasonable mortality rates in penetrating cardiac injuries[98, 117]

Penetrating cardiac wounds seen in civilian practice are due to knives ice picks bullets and other projectiles or rarely to inward displacement of ribs or sternal fragments Although in the past the majority of civilian cardiac wounds were the result of stabbings[18, 103, 105] gunshot wounds to the heart are now seen with increasing frequency[118] In military situations cardiac wounds are most commonly caused by high speed projectiles

Penetrating cardiac wounds are most often seen with wounds of the precordium but may be seen in association with wounds of other areas of the chest and with wounds of the neck and upper abdomen

The relative frequency of penetrating wounds to the various cardiac structures coincides with their relative area of exposure on the anterior chest wall In order of decreasing frequency, the right ventricle, left ventricle right atrium and left atrium are involved in penetrating wounds of the heart[105] Although much of the right coronary artery is anterior and exposed, it is injured less often than the left because the overlying sternum frequently serves as a natural protective barrier

Pathophysiology and clinical picture The pathophysiologic picture of penetrating wounds of the heart depends upon the mode site and size of injury and the state of the pericardial wound

In the cases in which the pericardial w... remains open and allows free drainage of intrapericardial blood the cardiac wound m... fests with symptoms and signs of hemorrhage hemothorax, whereas when the pericar... wound is obliterated with blood clot and ad... lung, prepericardial fat, or other structure escaping blood from the cardiac chamber c... drain into the pleural space and cardiac tamp... ade ensues Stab wounds are similar to surg... incisions and usually cause little cellular destr... tion adjacent to the wound Such wounds in relatively thick walled right or left ventricles ... spontaneously seal after various amoun... initial bleeding and may or may not be associa... with pericardial tamponade Because of the r... tively slow rates of bleeding in these wounds ... the minimal impairment of cardiac ac... frequently most of the blood accumulated i... pericardial sac is defibrinated and remains Small wounds of the thin walled atria may ... because of the lower pressure of the inj... chamber and commonly they present as the ... ventricular wounds or they may continue to b... slowly, producing cardiac tamponade or he... rhage and death If stab wounds of the heart ... large (greater than 1 cm) they bleed more bri... and either cardiac tamponade develops rapidly ... if the pericardial wound does not seal and bl... exits into the pleural space, massive hemotho... and hypotension develop Most of the bl... accumulated in the pericardial space in the... wounds is generally clotted owing to the inabilit... of the heart to defibrinate it because of the rate ... bleeding and the reduced cardiac movement F... these reasons pericardiocentesis in such wou... is frequently ineffective or its benefits shor... lived

Bullet wounds of the heart are associated with varying degrees of cellular destruction adjace... to the path of the missile depending on ... velocity These wounds are associated with more rapid and less frequently self limited bleeding Pericardial tamponade or hemorrhagic shock frequently develops rapidly For reasons simila... to those mentioned for large stab wounds, interpericardial blood is usually clotted and cardiocentesis of minimal lasting benefit

Coronary artery injuries depending on the ... of the vessel involved, may lead to various degrees of myocardial ischemia or even infarction...

Diagnosis Injury to the heart should be

...cted in the presence of a penetrating wound ... chest neck upper abdomen or particularly precordium, or if a missile traverses the ...astinum The majority of patients with pene... ...ng cardiac wounds (81 ... or 60 per ... ...) succumb shortly after injury from ...iac tamponade or massive bleeding Most of ...remaining patients present with symptoms ... signs of cardiac tamponade or hypotension ... hemothorax Rarely such patients will ...ent with only evidence of elevated central ...ous pressure In patients presenting with ...othorax and continuous bleeding the diag... ...s of penetrating cardiac injury is made at ...acotomy

...gitation lack of cooperation air hunger cool clammy skin neck vein distension Kuss...ul s sign paradoxical pulse muffled heart ...nds and elevated central venous pressure in ...ients with penetrating wounds of the precor...m neck, chest and upper abdomen strongly ...gest penetrating injury to the heart with ...aponade Although with these clinical find...s cardiac tamponade is relatively easy to ...gnose it may not be so in certain clinical ...tings When ethanol intoxication for example ...present it may produce many of the signs of ...mponade particularly the neurological mani... Such patients should be thoroughly ...ed and pericardial tamponade excluded ...fore the agitation and the lack of cooperation ... are attributed to the intoxication In patients ...th hemothorax and pericardial tamponade the ...inical picture may be attributed to just blood ...ss when volume expansion markedly improves ...he hemodynamic parameters In such patients ...owever cardiac tamponade should be strongly ...spected and searched for since volume expan...on which increases the filling pressure will ...sult in clinical improvement of patients with ...othorax and tamponade or tamponade ... Neck vein distension and/or a central ...enous pressure of 12 cm saline or greater in such ...nstances strongly suggest pericardial tamponade ...ther than hypotension due to blood loss ...though these signs may be misleading particu...larly when other conditions which may produce ...elevation of the central venous pressure are pres...nt

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in 1896[4] and pericardiocentesis in 1826,[95] the treatment of traumatic cardiac tamponade has varied. Presently multiple pericardiocentesis as a definitive mode of therapy is of historical interest only and although surgical repair, only in the face of recurrence of tamponade after one or two pericardiocenteses, has compared quite favorably with immediate surgical repair alone,[118] it should be discouraged.

The progressive improvement of transportation has resulted in prompt arrival of the more severe cardiac wounds which can be handled successfully only with immediate surgery. In addition the unpredictable course of traumatic pericardial tamponade following an initial favorable response to pericardiocentesis, coupled with the remarkable advancement in the fields of resuscitation, anesthesia, and cardiac surgery, strongly support the policy of immediate surgery for all patients with penetrating wounds of the heart.[11] Sometimes surgery should be immediate and in some cases in the emergency room with thoracotomy and repair of the injury. Pericardiocentesis therefore should be used only to provide a short time for the patient to be operated upon safely.

Thoracotomy is performed with general anesthesia administered via an orotracheal tube. Special attention must be paid here for two reasons. Peripheral vasodilatation which occurs with general anesthesia as well as decreased venous return occurring with positive pressure ventilation both reduce the filling pressure of the heart and accentuate the effects of pericardial tamponade. This may result in cardiac arrest before the pericardium is opened. For this reason general anesthesia should be very light so that the patient will require minimal positive pressure ventilation until the pericardium is opened.

The patient is placed in a supine position with the involved hemithorax elevated about 35 degrees. The entire chest from a posterior axillary line on the involved side to anterior axillary line on the uninvolved side is prepared and draped, including the base of the neck. A submammary incision is made which may be extended, if necessary, to the contralateral side. The pleural space is entered through the fourth intercostal space and, if tamponade is present, a tense bluish pericardium is exposed. Having available suction, sufficient blood for transfusion, and assistance for rapid exposure, the pericardium is opened and blood and blood clots evacuated. Bleeding from the heart is controlled by placing a finger o... wound or, if necessary, into the wound. Af... evacuation of blood and clots and cont... bleeding, the heart is left relatively undist... to regain normal action and restore perfusi... much as is possible before suturing. This red... the chance of precipitating ventricular fibrill... during the necessary cardiac manipulation. S... wounds are closed with interrupted su... placed below the wound occluding finger. Th... are tied as the finger is withdrawn. In proje... injuries where there is a surrounding area... damaged myocardium, mattress sutures ... Teflon or pericardial bolsters are used to prev... the sutures cutting through the damaged myoca... dium. Wounds in the proximity of the coro... arteries may be closed by placing horizo... mattress sutures through the myocardium b... neath the coronary artery to prevent occlusio... an injury to the artery in placing or tying ... sutures. Rarely projectiles may create a defect ... the cardiac wall which is difficult or impossible ... repair by suture approximation of the wou... edges. Under these circumstances, the wound ... best managed with or without a prosthesis a... establishing cardiopulmonary bypass.[110] Likew... posterior cardiac wounds may be best trea... after institution of cardiopulmonary bypass ... the lifting of the apex of the heart necessary ... exposure of such wounds is poorly tolerated.

Injury of a major coronary artery is repai... primarily or with the use of a vein graft. Sm... branches which are not amenable to anastom... are ligated.

After repair of the cardiac wounds, the hea... palpated for the presence of a thrill. No intra... diac defect thus discovered should be repaired ... this time, however, except in the very rare c... when the defect is of such magnitude that ... patient would not be expected to survive with... In such a case, cardiopulmonary bypass is in... tuted and the lesion repaired under direct vis... When a projectile is palpated, it is remove... accessible; if on the right side of the heart ... embolized into the pulmonary arterial t... Projectile embolectomy may then be perfor... at a future date when the patient's condi... permits.

Postoperative management is similar to tha... any other critically ill patient with ... determinations of hemodynamic para... strict attention to intake and outp...

illmarks of good care In addition the patient ould be closely observed through his hospital ay and later for the development of symptoms residual or delayed sequelae from the pene ating cardiac wound Many such sequelae may cur following penetrating trauma to the heart ich as posttraumatic or postoperative pericardi s, ventricular septal defect valvular defects entricular aneurysm aortocardiac aortopul onary or coronary artery to coronary vein or to ardiac chamber communication When such equelae are found appropriate medical and/or urgical treatment should be instituted If a ardiac defect is found which endangers the atient s life cardiac catheterization should be erformed as soon as possible and followed by urgical repair If the patient, however tolerates us lesion postoperatively cardiac catheterization hould be performed electively and the hemody ly significant defects be repaired

Injuries to the pericardium

The pericardium may be injured from blunt or etrating trauma and its injury may vary from tusion to laceration or rupture and to the ayed manifestations of pericardial injury i e pericarditis suppurative pericardi or constrictive pericarditis

Pericardial trauma commonly associated with or cardiac trauma is usually manifested by signs and symptoms of the coexisting cardiac ury Isolated contusions or small lacerations of pericardium are usually unrecognized how they may rarely lead to hemopericardium ardiac tamponade

Rupture of the pericardium from lethal or thal blunt chest trauma is quite frequent usually associated with cardiac injury ly however when an isolated lesion occurs linical manifestations are the result of hernia n of the heart through the pericardial

Posttraumatic pericarditis is a frequent compli of blunt or penetrating injury to the heart pericardium It may appear shortly the injury or days weeks or even months and it may recur

Fever sweats and precordial or retrosternal est pain radiating to the neck left shoulder or ular area are symptoms of posttrau pericarditis which may be intensified by deep inspiration or recumbency and relieved by sitting upright Friction rub is frequently heard and muffling of the heart tones and even paradox ical pulse may be present when a significant amount of pericardial fluid is accumulated

The course of posttraumatic pericarditis is usually self limited and the treatment is sympto matic initially with acetylsalicylic acid If this fails corticosteroids are administered Suppura tive or constrictive pericarditis[12] and delayed hemopericardium[28] are very rare late complica tions of trauma to the pericardium

REFERENCES

1 Committee on Trauma and Committee on Shock Acci dental death and disability The neglected disease of modern society Washington D C 1965 National Academy of Sciences p 5
2 Symbas, P N Traumatic injuries of the heart and great vessels, Springfield Ill 1972 Charles C Thomas Publisher
3 Borch, O Cited by Warburg E Subacute and chronic pericardial and myocardial lesions due to nonpene trating traumatic injuries A clinical study London 1938, Oxford University Press
4 Schnabel, H Intrapericardiales aneurysma aortae dissecans traumaticum bei gesunden Aortenwandung en Z Klin Med. N F 10 424 1859
5 Hewitt, P Rupture of the heart and large vessels, the result of injuries London Med Gaz. 4 (n.s.) 870 1847
6 Fischer G Die Wunden des Herzens und des Herzbeu tels, Langenbecks Arch. Klin Chir 9 571 1868
7 Kellert, E Traumatic rupture of the heart Report of a case with uninjured chest wall J Lab Clin Med. 2 726 1916-17
8 Clendy R E and White P D Nonpenetrating wound of the heart Rupture of papillary muscle and contusion of the heart resulting from external violence Case report, AM HEART J 11 366 1936
9 Leinoff H D Direct nonpenetrating injuries of the heart, Ann Intern Med. 14 653 1940
10 Leiberman J Lasky I I Dulkin L I and Lobstein O F Serum glutamic oxalacetic transaminase activity in conditions associated with myocardial infarction I Bodily trauma Ann Intern Med 48 485 1957
11 Kissane R W Traumatic heart disease Circulation 6 421 1952
12 Sigler L H Trauma of the heart due to nonpene trating chest injuries. Report of cases with recovery or long survival J A. M A. 119 855 1942
13 Hale, H W., Jr and Martin J W Myocardial contu sion Am. J Surg 93 558 1957
14 Osborn, G R. Findings in 262 fatal accidents Lancet 2 277 1943
15 Liedtke A. J and DeMuth W E Jr Nonpenetrating cardiac injuries A collective review AM HEART J 86 687 1973
16 Saphir O Rupture of the heart by indirect trauma in a four year-old boy Am J Med Sci. 173 353 1927
17 Stapp J P Gravitational stress in aerospace medicine Boston 1961 Little Brown & Company pp 168 188
18 Lasky I I Nahum, A M and Siegel A. W Cardiac injuries incurred by drivers in automobile accidents J Forensic Sci. 14 13 1969
19 Bright, E F and Beck, C S Nonpenetrating wounds

of the heart A clinical and experimental study AM HEART J 10 293 1934

20 Kissane R W Traumatic heart diseases especially myocardial contusion Postgrad Med 15 114 1954

21 Moritz A R and Atkins J P Cardiac contusion An experimental and pathological study Arch Pathol 25 445 1938

22 Pitts H H and Purvis G S Ruptured traumatic aneurysm in a child Can Med Assoc J 57 165 1947

23 Louhimo I Heart injury after blunt trauma Acta Chir Scand 1 (Suppl 380) 1968

24 DeMuth W E Baue A E and Odom J A Contusions of the heart J Trauma 7 443 1967

25 Watson J H and Bartholomae W M Cardiac injury due to nonpenetrating chest trauma Ann Intern Med 52 871 1960

26 Kissane R W Fidler R S and Doons R A Electrocardiographic changes following external chest injury to dogs Ann Intern Med 11 907 1937

27 Anderson R H Nonpenetrating injuries of the heart Br Med J 2 307 1940

28 Chapman M G and McEachern J A Cardiac contusion caused by use of a jackhammer AM HEART J 54 625 1957

29 Taylor H H Transient cardiac arrhythmia induced by nonpenetrating trauma to the chest AM HEART J 46 557 1953

30 Harthorne J W Kantrowitz P A Dinsmore R E and Sanders C A Traumatic myocardial infarction Report of a case with normal coronary angiogram Ann Intern Med 66 341 1967

31 Rosenson W Heart block in a child of ten years following trauma to the precordium Am J Dis Child 28 594 1924

32 Warburg E Traumatic heart lesions London 1938 Oxford University Press pp 1676 1868

33 Coffen T H Rush H P and Miller R F Traumatic complete heart block of 18 years duration with review of literature Northwest Med 40 195 1941

34 Scherf D Blumenfeld S and Yildiz M Experimental study on ventricular tachycardia and cardiac trauma Cardiologia 45 57 1964

35 Sims B A and Geddes J S Traumatic heart block Br Heart J 31 140 1969

36 Bharati S Chervony A Gruhn J Rosen K M and Lew M Atrial arrhythmias related to trauma to sinoatrial node Chest 61 331 1972

37 Reid J M and Baird W L M Crushed chest injury some physiological disturbances and their correction Br Med J 1 1105 1965

38 Dolara A Morando P and Pampaloni M Electrocardiographic findings in 98 consecutive nonpenetrating chest injuries Dis Chest 52 50 1967

39 DeMuth W E and Zinsser H F Myocardial contusion Arch Intern Med 115 434 1965

40 Wroblewski F The clinical significance of transaminase activities of serum Am J Med 27 911 1959

41 Shubin H and Weil M H Acute elevation of serum transaminase and lactic dehydrogenase during circulatory shock Am J Cardiol 11 327 1963

42 Vessell E S Feldman M P and Frank E D Plasma lactic dehydrogenase activity in experimental hemorrhagic shock Proc Soc Exp Biol Med 101 644 1959

43 Sleeman H K Simmons R L and Heistercamp C A Serum enzymes in combat casualties Arch Surg 98 272 1969

44 Ware R E Martin L G Tyras D H Kounas E and Symbas P N Coronary arterial injection of radioactive albumin microspheres in diagnosis of experimental myocardial contusion Surg Forum 23 1 1972

45 Martin L G Larose J H Sybers, R G Tyras, D H and Symbas P N, Myocardial perfusion imaging with ^{99m}Tc albumin microspheres, Radiology 107 1973

46 Moritz A R and Beck C S The production of a collateral circulation to the heart II Pathological anatomical study AM HEART J 10 874 1935

47 Parmley L F Manion W C and Mattingly T W Nonpenetrating traumatic injury to the heart, Circulation 18 371 1948

48 Desforges G Ridder W P and Lenoci, R J Successful suture of ruptured myocardium after nonpenetrating injury N Engl J Med 252 567 1955

49 Miller G E and Rue A E Blunt thoracic trauma producing heart laceration Ann Surg 166 852, 1967

50 Howat, R K Traumatic rupture of the heart Lancet 1 1313 1920

51 Stephens G A Three thoracic emergencies, Lancet 2 1382 1922

52 Ferris H W Traumatic rupture of the heart report of a case Arch Pathol 9 635 1930

53 Bogedain W Carpathios J Suu D V and Moore M F Traumatic rupture of myocardium Successful surgical repair J A M A 197 154 1966

54 Siderys H and Strange P S Rupture of the heart due to blunt trauma J Thorac Cardiovasc Surg 62 84 1971

55 Borja A R and Lansing A M Traumatic rupture of the heart A case successfully treated Ann Surg 171 438 1970

56 Pollock B E Markelz R A and Shuey H E Isolated traumatic rupture of interventricular septum due to blunt force AM HEART J 43 273 1952

57 Cary F H Hurst J W and Arentzen W R Acquired interventricular septal defect secondary to trauma Report of 4 cases N Engl J Med 258 355 1958

58 Rubenstein P and Levinson D S Acquired interventricular septal defects due to myocardial infarction and nonpenetrating trauma to the chest Am J Cardiol 7 277 1961

59 Miller D R Crockett J C and Potter C A Traumatic interventricular septal defect review and report of two cases Ann Surg 155 72 1962

60 Howard C P Aortic insufficiency due to rupture by strain of a normal aortic valve Can Med Assoc J 19 12 1928

61 Bushong B B Traumatic rupture of aortic valve Report of two cases one proved and another probable example of this condition Ann Intern Med 26 125 1947

62 Leonard J J Harvey W P and Hufnagel C A Rupture of the aortic valve A therapeutic approach N Engl J Med 252 208 1955

63 Proudfit W L and McCormack L J Rupture of the aortic valve Circulation 13 750 1956

64 Gregersen H Traumatic rupture of the aortic valve Report of a case Acta Chir Scand 129 669 1964

65 Najafi H Dye W S Javid H Hunter J A and Julian O C Rupture of an otherwise normal aortic valve Report of two cases and review of the literature J Thorac Cardiovasc Surg 56 57 1968

66 Frothingham C and Haas G M Rupture of normal chordae tendineae of the mitral valve AM HEART J 9 492 1934

Menges, H., Ankeney J. L. and Hellerstein H. K. Ruptured mitral chordae tendineae. Circulation 30 8 1964

McLaughlin, J. S. Cowley R. A. Smith G. and Matheson, N. A. Mitral valve disease from blunt trauma, J Thorac Cardiovasc Surg 48 261 1964

Bourain, Y. Four cases of rupture of the chordae tendineae of the mitral valve treated by valvuloplasty. Bull. Soc. Med. Hop. Paris 116 567 1965

Sanders, C. A. Scannell, J. G. Harthorne J. W. and Austen, W. G. Severe mitral regurgitation secondary to ruptured chordae tendineae. Circulation 31 506 1965

Szakaus, A. Traumatic rupture of papillary muscle with unrecognized cardiac tamponade. J Forensic Sci 11 1 4 1966

Jahnke, E. J. Nelson W. P., Aaby G. V. and Fitzgibbon, G. M. Tricuspid insufficiency. The result of nonpenetrating cardiac trauma. Arch Surg 95 880 1967

73. Morgan, J. R. and Forker A. D. Isolated tricuspid insufficiency. Circulation 43 559 1971

74. Madoff I. M., and Desforges, G. Cardiac injuries due to nonpenetrating thoracic trauma. Ann Thorac Surg 14 504 1972.

75. Cleland, W. P. Ellman, P., Goodman J., and Hallman A. Repair of ventricular septal defect following indirect trauma, Br J Dis. Chest 55 17 1961

76. Turney S. Z., Mathai, J. Singleton R. and Cowley R. A. Traumatic ventricular septal defect. Surgical repair in two patients. Ann Thorac. Surg. 13 36, 1972

77. Peirce E. C., Dabbs, C. H. and Rawson F. Isolated rupture of the ventricular septum due to nonpenetrating trauma, Arch Surg 77 87 1958

78. Stern, W. R. and Stoddard L. D. Traumatic interventricular septal defect of heart. Am Heart J 63 821 1962.

79. Stinson E. B. Rowles, D. F., and Shumway N. E. Repair of right ventricular aneurysm and ventricular septal defect caused by nonpenetrating cardiac trauma. Surgery 64 1022 1968

80. Gahagan, T., and Green H. W. Repair of complicated defect in cardiac septum after nonpenetrating trauma. J. A. M. A. 194 301 1965

81. Green L. Oakley C. M. Davies. D. M. and Cleland W. P. Successful repair of left ventricular aneurysm and ventricular septal defect after indirect injury. Lancet 2 984, 1965

82. Beall, A. C. and Shirkey A. L. Successful surgical correction of traumatic aortic valve regurgitation. J. A. M. A. 187 507 1964

83. Osborn, J. R., Jones, R. C. and Jahnke E. J. Traumatic tricuspid insufficiency. Hemodynamic data and surgical treatment. Circulation 30 217 1964

84. Bjork, V. P. Traumatic rupture of the tricuspid valves. Thoraxchirurgie 12 368 1965

85. Brandenburg, R. P. McGoon D. C., Campeau L. and Guilliani, E. R. Traumatic rupture of the chordae tendineae of the tricuspid valve. Am J Cardiol. 18 911 1966

86. Shabetai, R. Adolph, R. J. and Spencer F. C. Successful replacement of the tricuspid valve 10 years after traumatic incompetence. Am. J. Cardiol. 18 916 1966.

87. Salzer J. Weintraub R., Lower R. and Eldridge F. Isolated tricuspid insufficiency. Report of a cases with valve replacement, Am J Cardiol. 18 921 1966

88. Shean Mir g. L., Sako Y., and Alexander C. S. Traumatic tricuspid insufficiency. Am J Cardiol. 26 200 1970

89. Adams, F. Genuine works of Hippocrates, New York 1886, William Wood & Company vol. 2 p. 262

90. Boerhaave H. Aphorismi de Cognoscendis et Curandis Morbis (Aphorism 170) 1709 vander Linden p. 41

91. Paget, S. The surgery of the chest, London John Wright & Sons, Ltd p. 121

92. Bloch, M. H. Uber Wunden des Herzen und des Herzbentelf Verh. Dtsch. Ges Chir 11 108 1882

93. deVecchio S. Sutura del cuore Riforma Med. 2 79 1895

94. Rehn L. Ueber penetrirende Herzwunden und Herznaht, Arch. Klin Chir 55 315 1897

95. Riolanus, J. En cheiridium anatomicum et pathologicum, in quo ex naturali constitutione partium recessus a naturale statu demonstratur ad usum theatri anatomici adornatum, Lugd. Bat. A. Wyngaerden 1649

96. Dupuytren *cited by* Cazan G. M. Jr. Multiple laceration of the auricle U. S. Armed Forces Med. J. 3 253 1952.

97. Larrey D. J. Clin Chir Paris 2 284 1829

98. Elkin D. C. The diagnosis and treatment of cardiac trauma. Ann. Surg. 114 169 1941

99. Nelson H. Penetrating wounds of the heart. Arch. Surg. 47 571 1943

100. Cooper F. W., Jr., Stead, E. A. Jr., and Warren J. V. The beneficial effect of intravenous infusions in acute pericardial tamponade. Ann Surg 120 822 1944

101. Cooley D. A., Dunn, J. R., Brockman H. L., and De Bakey M. E. Treatment of penetrating wounds of the heart. Experimental and clinical observations, Surgery 37 882 1955

102. Bishop L. H., Jr. Estes F. H. Jr. and McIntosh H. D. Electrocardiogram as a safeguard in pericardiocentesis, J. A. M. A. 162 264 1956

103. Wilkinson A. H. Jr., Buttram T. L. Reid W. A., and Howard J. M. Cardiac injuries. An evaluation of the immediate and long range results of treatment. Ann Surg 147 347 1958

104. Isaacs, J. P. Sixty penetrating wounds of the heart. Clinical and experimental observations. Surgery 45 696 1959

105. VonBerg V. J. Moggi, L. Jacobson L. F., Jordan P., Jr. and Johnston C. G. Ten years experience with penetrating injuries of the heart. J Trauma 1 186, 1961

106. Beall, A. C. Jr. Ochsner J. L. Morris G. C. Jr. Cooley D. A. and De Bakey M. E. Penetrating wounds of the heart, J Trauma 1 195 1961

107. Blalock, A., and Ravitch, M. M. A consideration of the nonoperative treatment of cardiac tamponade resulting from wounds of the heart. Surgery 52 330 1962

108. Jones, E. W. and Helmsworth J. Penetrating wounds of the heart. Thirty years experience. Arch Surg 96 671 1968.

109. Hewitt, R. L. Smith, A. D. Jr. Weichert R. F. III and Drapanas, T. Penetrating cardiac injuries: current trends in management. Arch Surg 101 683 1970

110. Symbas, P. N. Tyras, D. H., and McCraw D. B. Repair of a left ventricular traumatic defect with a Dacron prothesis, J Thorac Cardiovasc Surg 63 608 1972

111. Beall, A. C. Jr., Patrick T. A., Okies J. E. Bricker D. L., and De Bakey M. E. Penetrating wounds of the heart. Changing patterns of surgical management. J Trauma 12 468 1972

112. Symbas, P. N. DiOrio D. A., Tyras, D. H. Ware R. E.

and Hatcher C R Jr Penetrating cardiac wounds Significant residual and delayed sequela J Thorac Cardiovasc Surg 66 526 1973

113 Anagnostopoulos C E and Kittle C F Penetrating wounds of the heart and great vessels A report of 30 patients Thorax 28 142 1973

114 Thaning N O and Hinder R A Penetrating stab wounds of the heart—experience with 23 cases S Afr J Surg 2 209 1973

115 Bolanowski P J P Swaminathan A P and Neville W E Aggressive surgical management of penetrating cardiac injuries J Thorac Cardiovasc Surg 66 52 1973

116 Hart R J Jr and Gregoratos G Ventricular septal defects caused by stab wounds Report of two cases Milit Med 289 1974

117 Trinkle J K Marcos J Grover F L and Cuello L M Management of the wounded heart Ann Thorac Surg 17 230 1974

118 Symbas P N Harlaftis N and Waldo W Penetrating cardiac wounds What appears to be the best management In preparation

119 Rea W J Suggs W L Wilson L O Webb W R and Ecker R R Coronary artery laceration An analysis of 22 patients Ann Thorac Surg 7 518 1969

120 Boyd T F and Strieder J W Immediate surgery for traumatic heart disease J Thorac Cardiovasc Surg 50 3 1965

121 Munchow O B G Carter R Vannix R S and Anderson F E Cardiac arrest during ventricle herniation Report of a case of two successful re... tions, J A M A 173 1350 1960

122 Hoffman K T Traumatic rupture of the pericard... with heart luxation Thoraxchirurgie 14 62, 1966

123 Tabatznik B and Isaacs J P Postpericardiot... syndrome following traumatic hemopericardium Am J Cardiol 7 83 1961

124 Goodkind M J Bloomer W E and Goodyer A V N Recurrent pericardial effusion after nonpenetrating chest trauma Report of two cases treated with adreno cortical steroid N Engl J Med 263 874 1960

125 Holswade G R Engle M A Redo S F Goldsmith E I and Barondess J A Development of ... diseases and a viral disease like syndrome after extracorporeal circulation Circulation 27 812 1963

126 Van der Geld H Anti heart antibodies in the postper icardiotomy and postmyocardial infarction syndromes Lancet 2 617 1964

127 Raker J W Langfeld S B and Gowen G F Traumatic hemopericardium producing late constrictive pericarditis Report of a case Ann Surg 148 ... 1958

128 McKusick V A Kay J H and Isaacs J P Cons... tive pericarditis following traumatic hemopericardium Ann Surg 142 97 1955

129 Mason L B Warshauer S E and Williams, P W Stab wound of the heart with delayed hemopericardium J Thorac Surg 29 524 1955

.hentolamıne

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ɔr many years phentolamıne was used prımarıly ‥ a screenıng test for the detectıon of pheochro ‥ocytoma Recent work however has demon ‥rated that the drug has far greater clınıcal pplıcatıon

hemıstry

Phentolamıne or 2 (N' p Tolyl N m hydroxy henylamınomethyl) ımıdazolıne hydrochlorıde ı the hydrochlorıde salt of an ımıdazolıne ompound related to prıscolıne Due to ıts alpha drenergıc blockıng propertıes ıt was first ınvestı ‥ as a potentıal hypotensıve agent ın the ‥nt of patıents wıth essentıal hyperten ıon However large doses of phentolamıne when ‥ed by the oral route over a prolonged ‥ tıme caused ıntolerable gastroıntestınal anıfestatıons Due to thıs clınıcal experıence ‥e drug was not used for many years

‥logıc actıons

Phentolamıne ıs known to be an alpha adrenergıc blockıng agent Thıs ıs based on the observatıon that ıt can antagonıze or even reverse the pressor response to epınephrıne[2,4] The blockade thus produced ıs relatıvely transıent A mıld sympatholytıc actıon becomes manıfest only wıth the use of very large amounts of thıs agent[5] The drug also has a perıpheral vasodılatıng effect whıch ıs not blocked by atropıne[6] The drugs relatıvely weak sympathetıc blockıng actıon as well as ıts antagonısm to the cırculatıng catecho lamınes cannot adequately explaın the strıkıng vasodılatıon that results from ıts use under normal restıng condıtıons Taylor and assocıates[7] belıeve that a dırect relaxıng effect on the vascular smooth muscle plays the domınant role ın the productıon of the conspıcuous vasodılata tıon However the recently descrıbed beta adrenergıc stımulatıng actıon of phentolamıne probably also contrıbutes to the perıpheral vaso dılatıon Thıs beta adrenergıc stımulatıng actıon ıs suggested by the observatıon that the fall ın blood pressure and the ıncrease ın cardıac rate produced by 5 mg of phentolamıne can be sıgnıf ıcantly blocked by the prıor admınıstratıon of propranolol[8] Propranolol can sımılarly block the ınotropıc and chronotropıc actıon of phento lamıne ın dogs.[10]

The possıble ınotropıc actıon of the drug may be explaıned by the recent observatıon of varıous workers Daırman and co workers[10] admınıstered phentolamıne (5 mg per kılogram) to rats At the heıght of alpha receptor blockade the conversıon of a tracer dose of tyrosıne C to norepınephrıne ın the heart braın and adrenal gland was ıncreased threefold wıth no alteratıon ın specıfic actıvıty of tyrosıne ın blood and tıssues From these studıes Daırman and assocıates[1] concluded that receptor blockade led to ıncreased synthesıs and release of norepınephrıne ın the three organs that were measured Thıs contentıon has receıved support from the recent work of Bagwell and assocıates[11] They admınıstered 5 mg per kılo gram of phentolamıne to seven experımental anımals and observed an ıncrease ın the left ventrıcular contractıle forces If the anımals were pretreated wıth reserpıne the ınotropıc actıon of phentolamıne could be blocked A subsequent ınfusıon of norepınephrıne could then restore the ınotropıc effect The authors concluded that the posıtıve ınotropıc actıon of phentolamıne ıs ındı rect and dependent on the release of norepıneph rıne In support of thıs contentıon phentolamıne has no dırect effect on contractıle or adenyl cyclase functıon ın denervated or reserpınızed ısolated preparatıons[2]

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Reprınt req ests Lawre c Gould M.D Dept. of Med cın The Methodıst Hosp tal, 506 Sıxth St B ooklyn N Y 11215.

In heart failure, there is suppression of insulin secretion Phentolamine produces an immediate and significant reversal of this insulin suppression Phentolamine can also increase the insulin secretion response in normal individuals [13] Thus phentolamine can support myocardial metabolism by this release of insulin suppression

Hemodynamic actions

The administration of 5 mg of phentolamine intravenously to normal dogs, each with a strain gauge attached to the right ventricle will increase the ventricular contractile force [14] When arterial pressure and heart rate are closely controlled the positive inotropic effect of phentolamine in the denervated dog heart can also be demonstrated [15] Similarly, in normal subjects and in patients recovering from heart disease the measurement of left ventricular dp/dt (max) is increased supporting the positive inotropic action of the drug [14]

The administration of this drug at an infusion rate of 0 3 mg per minute to patients in congestive heart failure produces a striking hemodynamic improvement The cardiac output cardiac rate and stroke index increase while the pulmonary artery pressure, systemic peripheral resistance left ventricular end diastolic pressure and left ventricular end diastolic volume fall [14] The increase in the ejection of blood from the heart is due to the result of positive inotropism and a reduction in afterload to contraction The latter occurs through primary vasodilatation and ease of runoff during systole Phentolamine was also administered to six patients in pulmonary edema [16] The drug was infused at a rate of 0 3 mg /min for an average duration of 30 minutes All of the patients demonstrated with treatment a moderate decline in the arterial pressure and prompt clinical improvement Majid and associates[15] administered phentolamine at a dose of 1 to 2 mg /minute to 12 patients in severe heart failure All had underlying coronary heart disease This resulted in a rapid relief of symptoms, with a substantial reduction in the left ventricular end diastolic pressure and pulmonary artery mean pressures and a significant increase in the stroke volume and cardiac output These changes were maintained throughout the three hour infusion Williams and associates[17] have recently compared nitroprusside versus phentolamine in the therapy of cardiac failure Phentolamine principally decreased afterload while nitroprusside decreased the preload and afterload A significant rise in the cardiac index was seen with phentolamine while a fall in this parameter was seen after nitroprusside infusion These workers concluded that phentolamine was more effective than nitroprusside on improving pump failure.

Use in myocardial infarction

Recently phentolamine has been used by several groups to improve left ventricular function Kelly and co workers[18] reported on a series of 11 patients with hypertension associated with acute myocardial infarction Phentolamine decreased the elevated left ventricular filling pressure while the cardiac index increased This was associated with only a small decrease in the arterial pressure These authors postulated that the myocardial oxygen demand was decreased and this reduced infarct size Chatterjee and associates[19] also demonstrated the beneficial hemodynamic action of phentolamine They observed that those patients with the highest filling pressure and lowest baseline cardiac output have the most beneficial improvement in hemodynamic performance These workers also suggested a reduction in the mortality rate of cardiogenic shock by the use of phentolamine. A recent study in our laboratory [a] revealed that phentolamine can improve cardiac performance even in patients with a normal or low arterial pressure Perret and co workers[21] have demonstrated that even an infusion of only 10 mg of phentolamine per hour can alleviate left ventricular failure complicating acute myocardial infarction The apparent mechanisms for the cardiac improvement are a decrease in afterload and positive inotropy There appears to be great promise for the use of phentolamine in this clinical setting

With the administration of phentolamine it is probable that the myocardial oxygen consumption remains relatively unchanged In support of this contention Nagasawa and associates[22] recently determined the myocardial oxygen consumption and the coronary blood flow in 11 dogs with an experimentally induced myocardial infarction These parameters were measured before and 20 minutes after an infusion of phentolamine—2 mg /Kg /min They observed that the myocardial oxygen consumption remained relatively unchanged while the coronary blood

v to ischemic areas increased Recently our up[3] administered phentolamine to eight ~ients with a recent myocardial infarction ile we determined the coronary blood flow ng the isotope Rb[6] The absolute flow cannot - determined with this method since individual ~iability in depth and size of the heart prevents absolute estimate of myocardial uptake of the ~ liotsotope The obtained value for myocardial arance of rubidium represents the mean flow unit mass and it is conveniently expressed per 0 G myocardium In all eight cases the ronary flow increased from a control value of 3 to the post phentolamine value of 117 L/min per 100 G of myocardium ($p < 0.01$) oronary artery dilatation or an increase in llateral flow to the myocardium have been ostulated as likely explanations for phentola ine s action

in arrythmias

In his experimental work on dogs Leimdorf r showed that the intravenous administra ion of phentolamine prevented nicotine sulfate nd epinephrine induced arrythmias and con erted methacholine induced atrial flutter fibril ation and atrioventricular nodal rhythm to iormal sinus rhythm He further demonstrated hat phentolamine administration prevented the ippearance of pronounced bradycardia during lectrical stimulation of the vagus nerve Vargaft hg and Coignet[6] demonstrated that the appearance of aconitine arrhythmia in rats was delayed by phentolamine Further ventricular fibrillation caused by chloroform inhalation in mice was blocked by phentolamine The antiar rythmic effect of phentolamine was investigated in ten normal dogs acutely digitalized with ouabain[7] Phentolamine was infused for an average of 10 minutes at 0 3 mg per minute Ventricular arrythmias were abolished in seven of eight cases and the rate was increased in one case with sinus bradycardia It was subsequently reported that the intravenous administration of phentolamine could successively suppress digi talis or non-digitalis induced ventricular prema ture beats in man[8] Similarly phentolamine infused at a rate of 0 3 mg /min for 15 minutes decreased or abolished supraventricular prema ture beats in 22 of 30 patients Antani and Srinivas[10] also administered phentolamine at 0 3 mg /min to 19 patients with ventricular prema ture beats In 14 patients the premature beats were abolished and in five their frequency was diminished A recent study demonstrated that the oral administration of phentolamine was also very effective in suppressing ventricular prema ture beats in cardiac patients without an acute myocardial infarction[11] Recently the effective ness of phentolamine therapy for the prevention of cardiac arrhythmias was determined in a double blind study of 39 patients with uncompli cated acute myocardial infarction[12] Fifty milli grams of phentolamine or placebo was adminis tered orally four times a day for five days Phentolamine afforded a highly significant pro tection from ventricular premature beats and supraventricular premature beats No side effects were seen with phentolamine therapy

There currently are crude and relatively insen sitive tests to measure blood levels of phentola mine—namely by gas chromotography liquid chromotography and colorimetrically Imhof[3] has demonstrated that after the oral ingestion of 40 mg of phentolamine the maximum blood level is attained in 30 minutes and there is no activity by 90 minutes In view of this short duration of action a 100 mg and a 150 mg slow release tablet has been developed and is currently being investi gated

Rosen and associates[3] have studied the electro physiologic effects of phentolamine in canine Purkinje fibers They observed that the drug can prolong the action potential duration and the effective refractory period as well as decrease the membrane responsiveness and conduction veloc ity The effect of phentolamine on atrioventric ular conduction was studied in patients using the His bundle electrogram technique A shortening of the A H interval which signifies an improve ment in A V conduction was found by two groups of workers[3, 16] This improvement in conduction is probably due to the release of catecholamines In view of these favorable studies it now seems reasonable to widen the clinical experience with this drug

Use in angina pectoris

Twelve patients with stable angina pectoris received a placebo for seven days and then oral phentolamine for an additional seven days[7] Administration of the drug prior to placebo was not feasible because the delay required for the effects of phentolamine to dissipate would have

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onic obstructive pulmonary disease without ͻplicating cor pulmonale [7] In view of the ılts of these studies continued investigation of ntolamine as a bronchodilator and as a monary artery dilator is warranted

mmary

The clinical uses of phentolamine have widened ce its introduction as an anti hypertensive nt The vasodilating action of the drug as well its positive inotropic effects have led to its use treating congestive heart failure Recently lamine has been used by several groups to iprove left ventricular function in acute yocardial infarction There appears to be great omise for the use of phentolamine in this inical setting

The drug given intravenously or orally can ippress ventricular premature beats and supra ntricular premature beats However the expe ence of phentolamine as an antiarrhythmic ent is still limited Similarly the relief of angina ectors by phentolamine requires confirmation) additional clinical studies

Phentolamine can be used as a provocative test ı idiopathic hypertrophic subaortic stenosis ince it does not produce cardiac arrhythmias it nay be safer than isoproterenol The comparative ffectiveness of phentolamine and isoproterenol n diagnosing I H S S is unknown

Phentolamine has been advocated for several years as a beneficial agent for the treatment of shock The experience is still limited to a few groups who have reported favorable results

Phentolamine has been used as a bronchodi lator and a pulmonary artery dilator The prelim inary reports appear favorable However contin ued investigation [redacted] warranted

A sensitive measurement of the blood levels of phentolamine is not available When this is accomplished further insight into the metab olism of this drug will be forthcoming

REFERENCES

1 Moyer J H and Caplovitz C The clinical results of oral and parenteral administration of 2 (N p tolyl N m hydroxyphenyl aminomethyl) imidazoline hydrochlo ride (regitine) in treatment of hypertension and an evaluation of the cerebral hemodynamic effects, Am Heart J 45 60 1953

2 Meier [redacted] Yonkman F [redacted] Craver B N and Gross R A new imidazoline derivative with marked arenolytic properties, Proc Soc Exp Biol Med 71 0 1949

3 Freis, E [redacted] Mackay J G and Oliver W F The effect of sympatholyti drugs in the cardiovascular responses to epinephrine and norepinephrine in man Circulation 3 254 1951

4 Gould L Zahir [redacted] and Shariff M Is phentolamine an alpha adrenergic blocker? J Clin Pharmacol 11 268 1971

5 Walker H A Heymans C Wilson S and Richardson A P The effect of C 7337 on carotid sinus reflex and on pressor and peripheral vascular action of epinephrine and norepinephrine, J Pharmacol Exp Ther 98 [redacted] 1950

6 Goodman L A and Gilman A The pharmacological basis of therapeutics ed 2, New York 1955 The Macmillan Company [redacted] 584

7 Taylor S [redacted] Sutherland G R, MacKenzie G J Staunton [redacted] P and Donald, K W The circulatory effects of intravenous phentolamine in man Circulation 31 41 54 1965

8 Zahir M and Gould L Phentolamine and beta adrenergic receptors J Clin Pharmacol 11 197 1971

9 Singh J [redacted] Hood W [redacted] and Abelmann W H Beta adrenergic mediated inotropic and chronotropic actions of phentolamine Am J Cardiol 26 660 1970

10 Dairman W Gordon [redacted] Spector S Sjoerdsma, A., and Udenfriend [redacted] Effect of the blockers on catecholamine biosynthesis, Fed Proc 27 240 1968

11 Bagwell E E Hilliard, C C Daniell [redacted] B Taylor P L and Walton R P Studies on the inotropic mechanism of phentolamine Am J Cardiol 25 83 1970

12 Taylor S H Phentolamine Workshop The Ciba Foun dation London Nov 25 1975

13 Majid P A Saxton C Dykes, J R W Galvin M C and Taylor S [redacted] Autonomic control of insulin secretion and the treatment of heart failure Br Med J 4 328 1970

14 Gould L Zahir M and Ettinger S Phentolamine and cardiovascular performance Br Heart J 31 154 1969

15 Majid P A Sharma B and Taylor S H Phento lamine for vasodilator treatment of severe heart failure Lancet 2 719 1971

16 Gould L Zahir M Shariff M and Giuliani, M Phentolamine use in pulmonary edema Jap Heart J 11 141 19 0

17 Williams D O Hilliard G K Cantor S A Miller R R and Mason D T Comparative mechanisms of ventricular unloading by systemic vasodilator agents in therapy of cardiac failure nitroprusside versus phento lamine Am J Cardiol 35 17, 1975

18 Kelly D T Delgado C [redacted] Taylor D R Pitt B and Ross [redacted] S Use of phentolamine in acute myocardial infarction associated with hypertension and left ventric ular failure Circulation 47 729 19 3

19 Chatterjee K Parmley W W Ganz W Forrester J Walinsky P Crexells C and Swan H J C Hemody namic and metabolic re ponses to vasodilator therapy in acute myocardial infarction Circulation 48 1183 1973

20 Gould L Reddy C V R Kalanithi, P Espina, L and Gomprecht [redacted] F Use of phentolamine in acute myocar dial infarction Am Heart J 88 144 1974

21 Perret C Gardaz J P Reynaert M., Grimbert, F and Enrico J F Phentolamine for vasodilator therapy in left ventricular failure complicating acute myocardial infarction Br Heart J 37 640 1975

22 Nagasawa, K Vyden J K Forrester J and Corday E Effect of phentolamine on cardiac performance and energetics in acute infarction Circulation 48(Suppl 4) 199 19 3

23 Gould L., Reddy C V R Blatt C J., Gomprecht R F and Hayt [redacted] B Phentolamine effects on coronary

prolonged the study excessively Exercise was performed at the conclusion of the two drug periods All of the patients developed angina with the stress of exercise while taking placebos The average time to develop angina was 208 seconds In comparison nine of the 12 patients were able to exercise longer after phentolamine The mean increment in exercise capacity was 95 seconds Four of the patients were now limited by fatigue rather than by angina following phentolamine None of the patients exercised less after phentolamine than after placebo Grandjean[1] also exercised patients with angina before and immediately after the intravenous administration of 3 mg of phentolamine He observed that phentolamine could decrease the extent of ST segment depression He also measured the wedge pressure during the exercise state and found that phentolamine could significantly decrease this pressure These preliminary observations should be corroborated by additional clinical studies

Provocative test in idiopathic hypertrophic subaortic stenosis

Phentolamine given intravenously increases myocardial contractility and reduces peripheral vascular resistance Both effects lead to worsening of the obstruction to left ventricular outflow and accentuation of the systolic murmur[16, 1] A 5 mg dose of phentolamine was given intravenously to 14 patients with idiopathic hypertrophic subaortic stenosis All of the patients responded with the characteristic alterations in the carotid pulse contour and with the intensification of the systolic murmur Isoproterenol is the provocative drug commonly used in this condition However this agent can produce serious cardiac arrythmias There has been no study comparing the relative merits of isoproterenol and phentolamine in diagnosing I H S S

Use in shock

Phentolamine has been administered at 0 6 mg /minute to 20 patients in shock[40] In the seven patients with cardiogenic shock phentolamine increased the cardiac output and reduced the peripheral resistance This was associated with an increase in oxygen delivery to the tissues and reversal of anoxic metabolism However the reduction in arterial pressure from a mean value of 65 to 55 mm Hg limited the drug's clinical applicability The same group administered phentolamine to patients in shock due to hypovol[illegible] and bacteremia The predominant cardiac ef[illegible] was a decrease in the mean arterial pressure [illegible] only a minimal increase in the cardiac outp[illegible] This group of patients did not benefit f[illegible] phentolamine therapy If one administers 0 3 [illegible] per minute of phentolamine to such patients, o[illegible] might expect an increase rather than a fall in th[illegible] systemic pressure This hypothesis has bee[illegible] tested in eight dogs in hemorrhagic shock Phe[illegible] tolamine, infused at 0 3 mg per minute, produce[illegible] a rise in the mean femoral artery pressure as w[illegible] as an increase in the cardiac output[41] Althou[illegible] phentolamine has been advocated as a benefi[illegible] agent in shock for several years addition[illegible] studies are still required to evaluate the dr[illegible] usefulness in this condition

Use in lung disease

Phentolamine has an antispasmodic action in the isolated guinea pig lung[4] The administration of phentolamine in a dose of 10 mg per kilogram exerts a prophylactic action in cases of histamine and allergic bronchial asthma in the guinea p[illegible] as well as a curative action in the case of histamin[illegible] bronchial asthma In ten patients with an extrinsic type of bronchial asthma the fall in the vital capacity and forced expiratory volume in one second produced by histamine could be inhib[illegible] ited by the prior injection of phentolamine[42]

One study has shown a significant improvement in the vital capacity 1 and 3 second forced expiratory volume and maximum voluntary ventilation in 27 normal subjects as well as in 4[illegible] patients with chronic pulmonary emphysema when a nebulizer containing 5 mg of phentolamine in 1 c c of water was used[44] A comparable degree of improvement was observed in the same subjects when a nebulizer containing isoprotere[illegible] nol was used Marcelle[45] administered 5 mg o[illegible] phentolamine by inhalation to six patients i[illegible] status asthmaticus A rapid and lasting suppres[illegible] sion of the bronchospasm was observed eve[illegible] though other spasmolytics had been of no avail Not only is the drug a bronchodilator, but [illegible] potent pulmonary artery dilator When phentol[illegible] amine was administered intravenously to te[illegible] patients with cor pulmonale a 35 per cent fall i[illegible] the mean pulmonary artery pressure and a 22 pe[illegible] cent fall in the pulmonary vascular resistance wa[illegible] observed[46] A comparable hemodynamic improve[illegible] ment has also been demonstrated in patients wi[illegible]

ither optimal nutrition?

a Symposium on Obesity held in London Butterfield ntly recounted that one of my paediatric friends has es in his department which weigh from 5 to 20 pounds en he started to use them almost all the one year babies ld be weighed on those scales now not all the six month es can be weighed on them. In Britain it has been stated t up to one third of babies are too fat and although the portion falls, it rises to 20 to 30 per cent in adolescence In cent study undertaken on German schoolchildren calorie akes were found to be 5 to 15 per cent beyond recommended wances of children studied 47 per cent were stated to be rweight. In Britain from an examination of a large series children in 196? mean triceps skinfold of boys of 17 years raged 7.5 mm by 1966-67 the value had increased to 8 5 n.—a rise of 13 per cent in a 4 to 5 year period

This trend of steadily increasing weight for age has been ralleled by a trend steady although slowing down of reasing height for age But the former has outstripped the tter so that prevalences of overweight and obesity are rising white children Furthermore prevalences are also rising though at a slower rate in children in developing popula ons, more especially among those in urban areas. Can this end of rising weight for age be arrested or if not restrained? wo factors militate against control. First the present pala ible diet may well become even more palatable Second level f everyday physical activity is likely to decrease still further mong the groups of children mentioned as they grow older hat will the obesity situation be once they join the ranks of hat Passmore[4] has termed *Homo sedentarius*?

Tanner and Whitehouse veteran workers in this field in eferring to the increase in triceps skinfold insist that pupils it the new fiftieth percentile which corresponds with the old ifty fifth to sixtieth percentile are not at the optimal Uncertainty over the optimal in this and other aspects of anthropometry as they relate to present and future health, is indeed humbling Why should this be? The Boston and Iowa standards for weight and height were reported on pupils in 1943 and 1945 respectively Unfortunately the health patterns these pupils now experience are not known Measurements and observations should of course have been continued as on going studies—analogous to the long term and eminently fruitful investigations on adults that have been carried out at Framingham Tecumseh, and Evans County The pupils concerned are now middle aged. Understandably what is urgently needed is information on the *current* preva lences not only of obesity but of hypertension glucose intolerance hyperlipidemia diabetes etc in the various percentiles as they prevailed at the times of measurement In the virtual absence of such information is it justifiable as raised elsewhere to regard children in the lower percentiles of growth standards, i.e the underweight and short statured as having, *ipso facto* inferior health status?

To throw more light on this problem we have been carrying out studies on the health status of South African Negro children. The particular groups investigated were according to orthodox standards, very underweight namely those below the third percentile of weight for age i.e., less than 80 per cent of the fiftieth percentile of Boston standards. In local pre school children the proportion below the third percentile among whites is 2 to 8 per cent But among urban Negro preschool children the figure is 20 to 25 per cent Evidence local and from other parts indicates that the health status of such children (e g in respect of infection rate) is inferior to that of children *above* the third percentile Preschool children *below* the third percentile are therefore regarded as being in need of supplementary feeding Among *older* Negro children however the proportion below the third percentile actually is higher In preadolescent pupils the proportion affected is over a half although there is a decrease to 10 to 15 per cent by 17 years A high prevalence of underweight from 7 to 12 years has also been observed in Brazil and Jamaica Is this large segment of *older* children therefore at a demonstrable health disadvantage? Should it be mandatory for them to be given extra food as for example provided by school meals? In terms of orthodox nutrition the answer unequivocally is yes On the other hand among these older children are we quite certain that their health status is seriously prejudiced from insuffi ciency of nutrients?

One population of schoolchildren which we studied lived in an isolated mountainous region near Blyde River Canyon Eastern Transvaal Of pupils 10 to 12 years, 38 per cent were below the third percentile From attendance records kept over a 6 month period absenteeism averaged 5 per cent (staying away is not always for sickness) but the figures for the moieties above and below the third percentile did not differ significantly Another aspect investigated concerned the distance travelled in attending school, since some pupils lived nearby and others walked tremendous distances as much as 10 to [illegible] miles daily But in this variable as with absenteeism there were approximately the same proportions below and above the third percentile in the moieties who lived near or far from school As a check on those who walked long distances we arranged on one occasion for certain groups to be accompanied home by white students The latter observed that the Negro pupils maintained much the same pace whether ascending or descending mountainsides furthermore the pupils experienced less marked changes in pulse rate than the students who had deemed themselves fit In investigations in another area Komatipoort Eastern Transvaal on school children aged 10 to 15 years, subdivided into those with and without schistosomiasis we obtained data on maximum oxygen consumption rate (derived from 12 minute walk run races) and on school progress the mean scores in the moieties below and above the third percentile did not differ signifi cantly The same lack of discrimination prevailed in respect of hematological values, protein fractionation and other labora tory data

Certainly rural Negro schoolchildren accustomed to their frugal diet and active manner of life when opportunity offers are extremely happy to receive palatable foods and drinks

blood flow in humans with recent myocardial infarction Br Heart J 37 647 1975
24 Leimdorfer A Prevention and abolition of cardiac arrythmias by regitine Am J Physiol 171 742 1952
25 Leimdorfer A Abolition of cardiac arrythmias by regitine Arch Intern Pharmacodyn Ther 96 249 1953
26 Vargaftig B and Coignet, J L A critical evaluation of three methods for the study of adrenergic beta blocking and anti arrythmic agents Eur J Pharmacol 6 49 1969
27 Ettinger S Gould L Carmichael J A and Tashjian R J Phentolamine—use in digitalis induced arrythmias AM HEART J 77 636 1969
28 Gould L Zahir M Shariff M and Giuliani M D Treatment of cardiac arrythmias with phentolamine AM HEART J 78 189 1969
29 Gould L Umali F Colinbarranco M and Gomprecht R F Control of supraventricular premature beats with phentolamine J Clin Pharmacol 12 306 1972
30 Antani J A and Srinivas, H V Clinical evaluation of phentolamine in cardiac arrythmias Indian Heart J 24 25 1972
31 Gould L Gomprecht R F and Zahir M Oral phentolamine for treatment of ventricular premature contractions Br Heart J 33 101 1971
32 Gould L Reddy C V R Weinstein T and Gomprecht R F Antiarrythmic prophylaxis with phentolamine in acute myocardial infarction J Clin Pharmacol 15 191 1975
33 Imhof P Phentolamine workshop The Ciba Foundation London Nov 25 1975
34 Rosen M F Gelband H and Hoffman B F Electrophysiologic effects of phentolamine on canine Purkinje fiber Am J Cardiol 26 657 1970
35 Gould L Reddy C V R and Gomprecht R F The effect of phentolamine on atrioventricular conduction in man Chest [redacted] 158 1974
36 Khan A H Boughner D R, and Haider R Effect of phentolamine on atrioventricular conduction in man assessed by recording His bundle potential, Br Heart J 34 1102 1972
37 Gould L Reddy C V R and Gomprecht, R F Oral phentolamine in angina pectoris Jap Heart J 14 3.. 1973
38 Grandjean T Phentolamine Workshop The Ciba Foundation London Nov 25 1975
39 Moreyra E Buteler [redacted] Madoery R and Aldao L Drugs and maneuvers in the diagnosis of muscular subaortic stenosis AM HEART J 83 431 1972
40 Da Luz P L Shubin H, and Weil M H Effectiveness of phentolamine for reversal of circulatory failure Critical Care Med 1 135 1973
41 Gould L Ettinger S Carmichael A Lord, P and Hoffstra P The use of phentolamine in experimental hemorrhagic shock Angiology 21 330 1970
42 Wisniewska J M Prophylactic action of regitine in experimental histaminic and allergic bronchial asthma Arch Intern Pharmacodyn 149 56 1964
43 Kerr J W Govindaraj M and Patel K [redacted] Effect of alpha receptor blocking drugs and disodium cromoglycate on histamine hypersensitivity in bronchial asthma Br Med J 2 139 1970
44 Gould L and DiLieto M Phentolamine new bronchodilator N Y State J Med 70 2337 1970
45 Marcelle R Traitement de l etat de mal asthmatique par la phentolamine Acta Allerg 24 437 1969
46 Gould L DeMartino A Gomprecht R F Umali F and Michael A Hemodynamic effects of phentolamine in cor pulmonale J Clin Pharmacol 12 153, 1972
47 Gould L DeMartino A and Gomprecht R F Hemodynamic effects of phentolamine in chronic obstructive pulmonary disease Br Heart J 33 445 1971

the family of the sick

concern, consideration love and attention of the family he sick member transcend almost all human relationships the bedside manner of the compassionate family doctor these days of gadgetry many unnecessary complex impres- hazardous and often frightening procedures and special centers with their extensive formalities and rules and lations of family visiting can be upsetting The physician s rest too often seems to be primarily concerned with the and operation of complex frightening awful apparatus stern serious and grim automatons in attendance The scious dying patient needs his family at the bedside to hear last words and wishes and to offer assurances that those behind will be protected in his absence and all will be well the future Unfortunately in too many instances the ient sees the members of his family only briefly receives a or pat on the hand and is left alone to the monotonous of oxygen and suction apparatus flicking and ticking itors, and the grim tired attendants who are burdened h patients and often with many of their own problems as go about their daily routine bored and self satisfied with completeness of their knowledge With the approach of th, the family in the family room tired tense and lpless while humbly and quietly accepting the rules of the cial care centers always hoping for the best must think d wonder if modern medicine and science require this non mane discipline to assure recovery of their loved one And en death occurs then the family everlastingly wonders how ir loved one died What was on his mind at the time? Was great pain was he contented did he accept death well d what about his intended departing words wishes, and ce prior to lapsing into final coma and death?

The human side of medicine seems to be gone (hopefully not forever) displaced by fancy medicine A master doctor should know when he has much to offer and needs "fancy gadgetry and when these gadgets have little or nothing to offer He should be able to apply the Golden Rule at all times—even to the dying. He should not only encourage the presence of the family but he should engage their assistance and comforting influence and make use of family type care The family *must* participate actively in the care of the sick and certainly of the dying patient who is about to pass into the final eternal state The master physician quickly learns personalities capabilities and positive helpful roles of various members of the family in their care of the sick. Surely the concern of the family can annoy the doctor at times but this is part of caring for the sick, part of the practice of medicine The master clinician manages this extremely well He visits with the family regularly and for as long as necessary He escorts the family to the patient s bedside and remains with them for some time There is no hurry And he always arranges for the family to be with their dying relative A close caring relative in the room of the sick is a strong therapeutic tonic When possible it is even advisable to let such a person sleep in the patient s room And *best* of all by far treat the patient at his home This management is superior unless hospitalization is absolutely necessary

An attending, loving family is the greatest tonic for the sick. The dying patient should be contented if not happy He should die contented and not alone

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emperature and the incidence of acute myocardial infarction n a temperate climate

Mortality from acute myocardial infarction (AMI) has been shown to undergo seasonal variation in different climatic regions and it has been further suggested that this variation is due to temperature changes leading to thermal stress To test effects of seasonality and temperature in a southern temperate maritime climate a six year study of the incidence of acute myocardial infarction utilized the records of 1,036 patients admitted to the coronary care unit of the Royal Hobart Hospital with a diagnosis of acute myocardial infarc tion. The Unit serves an urban population of 150 000 and a rural hinterland of an additional 75 000 in the southeast of Tasmania and a previous survey has shown that 95 per cent of patients with AMI are admitted to this unit With the exception of patients dying before admission almost all patients with an AMI in the area are included The diagnosis of AMI was made on the usual historical electrocardiograph ic and enzyme criteria

Tasmania lies in a belt of prevailing westerly winds of the Southern ocean and this is the dominant factor in the climate For its latitude 43 S the island has abnormally mild winters and cool summers implying a small annual range of tempera ture By definition this is a temperate climate The weather is characterized by a continuous series of anticyclonic circula tions passing across the region from west to east at time intervals of around one week These short term alterations give Tasmania remarkably changeable day to day weather

In this climate the effects of seasonality and temperature upon AMIs are portrayed by the 72 consecutive monthly re cords of AMI admissions (with a mean of 14 4 cases per month) Fig. 1 shows that although there are slight variations

such as white children consume every day At one region near Rustenburg we carried out nutrient absorption studies involving 5 day balance observations on Negro pupils 10 to 12 years old 50 per cent of whom were below the third percentile different groups were given daily helpings of butter cheese baked beans skim milk jelly wholemeal bread and jam honey and Coca Cola According to information given by the children and the supervising teachers as well as evidence from balance observation data it was clear that these extra foods which supplied 200 to 500 calories daily were eaten *in addition to* the food in their everyday diet This behavior of course is likely to be in measure a temporary phenomenon yet the foregoing are the foods together with meat whose consumptions by Negro children and adults are rising with increase in socioeconomic state especially among families in urban areas At present among Negro adults in cities we have found that prevalences of obesity also hypertension far exceed those prevailing among age matched white adults

The point we wish to emphasize is that none of the rural Negro schoolchildren studied went hungry or was short of calories as supplied by their staple everyday foods (maize products bread beans wild spinaches meat once or twice weekly) Their diet and manner of life evoked the anthropometrical picture we observed Yet pupils below the third percentile—a large proportion of the total—displayed satisfactory performances in respect of school attendance educational progress ability to traverse long distances to and from school etc In like manner the diet and manner of life of white children evoke *their* anthropometrical picture with its rising prevalences of overweight and obesity It is questionable whether anything can alter this trend or even that becoming increasingly manifest among more privileged Negro children

While investigations on the Negro schoolchildren below the third percentile revealed no disadvantage in the respects specified this obviously does *not* imply that their present nutritional status and future health prospects give no cause for apprehension Some pupils even those able to walk long distances regularly and apparently without hardship were very thin Presumably their optimal weight for age lies at a percentile higher than the third but certainly lower than the fiftieth

Our observations while limited and far from exhaustive underline how inadequate is our knowledge regarding nutrition growth and their ramifications in future health We need to know more of the range of weight for age during growth (1) *below* which the enjoyment of good health is unequivocally impaired (2) *above* which no additional health benefit is conferred and (3) still further *above* which excessive weight constitutes a present and certainly a future handicap to health The foregoing lack of knowledge applies correspondingly not only to growth but to many other variables for example hemoglobin concentration we know neither the precise level below which ill health is undoubted nor the level above which higher iron intakes and higher hemoglobin concentrations result in no additional clinical benefit In another field the important physiological process of lactation there is uncertainty over the low level of nutritional intake below which milk yield and composition are significantly prejudiced also the level of nutritional intake above which additional food is without benefit to lactation

While discussion of the optimal in nutritional intake may seem currently unrealistic this is no reason why we should not seek to obtain more knowledge on the subject In the not so far distant future when population numbers seriously exceed available food supplies, it will be imperative to know m nd the minimum nutrient intakes which are compatible with the acquiring and maintenance of good health.

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REFERENCES

1 Butterfield W J H Summary *in* Burland, W L Samuel P D and Yudkin J editors Obesity London 1974 Churchill Livingstone p 366
2 Leading Article Nature and nurture in childhood obesity Br Med J 2 706 1975
3 Maaser R and Droese W Overnutrition in West German children Lancet 2 545 1971
4 Tanner J M and Whitehouse R H Standards for cutaneous fat in British children Br Med J 1 446 1962
5 Tanner J M and Whitehouse R H Revised standards for triceps and subscapular skinfolds in British children Arch Dis Child 50 142 1975
6 Passmore R The regulation of body weight in man Proc Nutr Soc 30 122 1971
7 Vickers V S and Stuart, H C Anthropometry in the pediatrician s office Norms for selected body measurements based on studies of children of north European stock J Pediatr 22 155 1943
8 Jackson R L. and Kelly H G Growth charts for use in pediatric practice J Pediatr 27 215 1945
9 Walker A R P and Richardson B D International and local growth standards Am J Clin Nutr 26 89 1974
10 Walker A R. P The short statured child Br Med J 1 454 1975
11 Richardson B D Malnutrition an unappreciated at risk group Trans R Soc Trop Med Hyg in press
12 Wittmann W Moodie A D Fellingham S A and Hansen J D L An evaluation of the relationship between nutritional status and infection by means of a field study S Afr Med J 41 664 1967
13 Guitti J C S Estudo sobre a condicao nutritive de uma populacao infantil da cidade de Londrine PA Brazil Rev Saude Bull 8 67 1974
14 Tizard J Three dysfunctional environmental influences in development Malnutrition non accidental injury and child minding Postgrad Med J 51(Suppl 2) 19 1975
15 Walker A R P Walker B F and Richardson B D Studies on schistosomiasis in a South African Bantu schoolchild population Am J Trop Med Hyg 19 9.. 1970
16 Walker A R P Studies on the effect of high crude fibre intake on transit time and the absorption of nutrients in South African Negro schoolchildren Am J Clin Nutr 28 1161 1975
17 Walker A R P Unpublished observations
18 Elwood P C The clinical evaluation of circulating haemoglobin level Clin Haematol 3 705 1974
19 Report of Expert Committee Nutrition in pregnancy and lactation WHO Tech Rep Ser No 302 Geneva, 1965 World Health Organization.

-ed to temperature and that only outside some ideal for human existence does thermal stress become a -ant factor It further seems likely that because of well i variations of heat tolerance by human communities will be found to be different optima of climate for nt ethnic groups.

) further observations with regard to the Tasmanian consistent with such a latitude temperature L Firstly in Tasmania neither the maximum nor the num daily temperatures were sufficiently high or low to a significant stress, whereas the maximum temperatures led in New Orleans and the minimum temperatures ded in Finland are well outside the range recorded in rt, and it is possible that these extremes of temperature eeded to cause a thermal stress. This would suggest that outside some temperate range would thermal stress me a significant factor Secondly the duration of the nal stress may not have been sufficiently prolonged since highly changeable weather pattern tends to ent sustained periods of either high or low temperature g recorded. De Pasquale and Burch have already ested that thermal stimulus has a cumulative effect and a prolonged duration of the stress is necessary before an t is seen Cumulative thermal stress is consistent with mania s winter seasonal AMI correlation

urther work on this old idea of optimum physical condi or each human race would require closer definition of natic regimes as well as detailed medical studies on a strictly comparable basis from a variety of localities As increasing numbers of people in the west at least gain partial control over the temperatures in which their lives are spent knowledge of the optimum should provide one means towards lessening human suffering.

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REFERENCES

1 Davies, J L. ed. Atlas of Tasmania Lands and Surveys Department, Tasmania 1965 p 3
2 De Pasquale N P and Burch G E The seasonal incidence of myocardial infarction in New Orleans, Am J Med. Sci. 242 468 1961
3 Sotaniemi, E Vuopala U., Huhti, E and Takkunen J Effect of temperature on hospital admissions for myocardial infarction in a subarctic area Br Med J 4 150 1970
4 Rose G Cold weather and ischaemic heart disease Br J Prev Soc. Med. 20 97 1966
5 Bull G M Meteorological correlates with myocardial and cerebral infarction and respiratory disease Br J Prev Soc. Med 27 108 1973.
6 Anderson, T W., and Le Riche W H Cold weather and myocardial infarction Lancet 1 291 1970

The effect of pregnancy on the midsystolic click and murmur of the prolapsing posterior leaflet of the mitral valve

he syndrome of a midsystolic click, late systolic murmur MSC-LSM) resulting from prolapsing of the posterior leaflet f the mitral valve continues to receive a great deal of nthusiastic interest, as reflected by the number of manu cripts and review articles appearing in the cardiology litera ure In spite of this, very little has been published concerning he MSC-LSM syndrome in pregnancy

In the past year we have seen three patients, ages 21 to 24 with the typical auscultatory findings of the MSC-LSM syndrome manifested by hemodynamically mild mitral insufficiency clinically and normal chest x rays and electrocardiograms, whose click and murmur were altered during gestation. In two of the three patients, the systolic click and late systolic murmur of mitral insufficiency disappeared while in the third patient only the click persisted in the third trimester of pregnancy In all three cases the auscultatory henomenon returned when re-examined three months post Review of the older literature reveals that murmurs ther heart sounds develop or disappear during pregnancy or immediately postpartum.

The effect of pregnancy on the intensity of the murmurs of aortic and mitral regurgitation have been previously noted by Marcus and colleagues In the majority of their patients the murmurs of aortic and mitral regurgitation decreased or became inaudible during pregnancy The diminished intensity or disappearance of the murmurs of mitral insufficiency and the auscultatory phenomenon of the MSC-LSM syndrome is probably related to reduction in peripheral vascular resistance known to occur with pregnancy The changes in the volume of mitral regurgitation and the intensity of the murmur of mitral insufficiency can be demonstrated at the bedside by altering peripheral vascular resistance through such maneu vers as squatting methoxamine infusion or amyl nitrite inhalation. Fontana and colleagues have shown the produc tion or the *intensification* of the murmurs of mitral regurgita tion through assumption of the erect posture in the MSC-LSM syndrome These changes were attributed to a reduction in the left ventricular end diastolic volume with shortening of the long axis of the left ventricle secondary to a decrease in the venous return thereby placing the mitral leaflets in a position of exaggerated prolapse As a result the mitral insufficiency increased and the systolic click moved

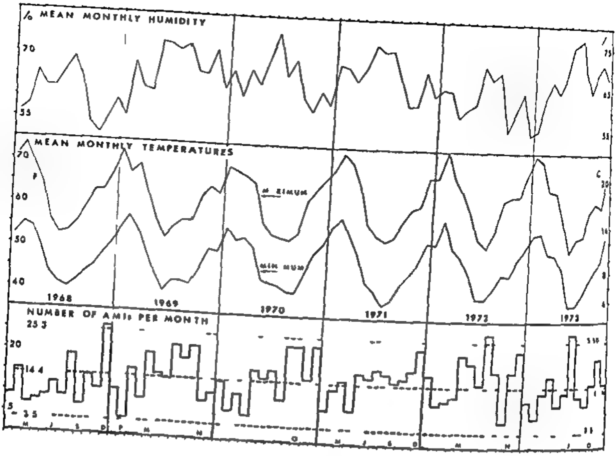

Fig 1

in the monthly number of admissions only three of these 72 monthly variations separately are significant at the ±2 S D level December 1968 August 1972 and July 1973 The mean monthly maximum and mean monthly minimum tempera tures and the mean monthly humidity are also graphed Values of correlation coefficients (*r*) coefficients of determi nation (r^2) and the probabilities of the correlations occurring by chance (*p*) for each climatic factor severally against the monthly figure of AMIs have been calculated While humidity may be ignored as a factor the r values suggest with a high degree of confidence ($p < 0.01$) that temperature is of impor tance such that lower values of both mean monthly maximum and mean monthly minimum (which are of course closely inter correlated) correlate with higher frequency of AMI In fact 9 7 per cent of monthly variation of AMIs is attributable to mean maxima and 12 6 per cent to minima of temperature This implies that some 90 per cent of AMIs are attributable to other factors but also corroborates other indications in Tasmania of winter peaking in heart disease conditions

In view of the changeable nature of weather in Southern Tasmania mean monthly figures might however be an inappropriate measure to show fine relationships with temper ature Actual daily values might be of greater importance The frequency of occurrences of each specified daily maximum and minimum temperature for the six year period were accumu lated into 10 F (5 56° C) classes together with the total number of AMIs recorded on each day with those tempera tures Rates of AMIs per day were closely similar regardless of temperature maxima or minima Testing both by χ and by Poisson distribution indicated no statistically significant vari ation of AMI with daily maximum or with daily minimum temperatures

A third hypothesis was that thermal stress and conseq AMI might be provoked by an acute temperature change de fined as a change of temperature within 24 hours of either 5 F (2 83 C) or 3° F (1 67° C) higher than the previous day maximum or 5° F or 3 F lower than the previous day minimum The total number of days with recorded AMIs and the total number of AMIs recorded on days showing an acute temperature change showed by χ^2 test that there is no significant relationship between AMIs and acute change da either at 5 or at 3 F of temperature change in 24 hours

Temperature has been said to influence the frequency of AMI by a number of authors In the sub tropical region of New Orleans at latitude 30 N the incidence of AMI increases in summer while in a sub arctic climate in Finland latitude 60 N the incidence is reversed with high incidence in winter months with temperatures below 14° F (−10 C)[1] An increased incidence in the mortality rate from ischemic heart disease in winter also occurs in the British cool temperate maritime climate about latitude 54 N [4] On the other hand in Ontario at latitude 44 N in a temperate but continental type of climate no seasonal variation in the mortality rate of ischaemic heart disease is found In Tasmania (latitude 43 S) a weak monthly variation in the frequency of AMI with a winter peak is now reported but no variation of AMIs with daily maxima or minima or with acute temperature change is noted

The similarity between these Tasmanian data and those reported by other authors suggests a generalized latitudinal gradient of AMI with a striking over all consistency The model seems to be characterized by a bi modal experience of thermal stress In high cold latitudes extreme cold is harmful and in low hot latitudes heat is damaging This also implies that at some midway optimum of temperate climate AMI is

liac effects of diphenylhydantoin isoniazid propylene glycol

e Editor

the March issue of AMERICAN HEART JOURNAL, Zoner and associates reported a case of Sudden death following venous sodium diphenylhydantoin " I would like to add points to their discussion.

he first point pertains to the cardiac effects of Dilantin s nt. Dilantin like diazepam is such an insoluble pound that it requires formulation with a 40 per cent ylene glycol solution. An important point to remember n using Dilantin intravenously is that the solvent, propy glycol, and Dilantin have both been reported to produce otension, bradycardia, and electrocardiographic changes.[2] litional side effects of propylene glycol reported in one ly include depression of the SA node multifocal ventric rrhythms, and, in very large doses asystole Alterations in ECG which have been attributed to the solvent include an reased amplification of the QRS and T waves The two chanisms proposed for these effects are a vagal and direct on the myocardium

Dilantin has been found to overshadow and prevent most of side effects of the propylene glycol but the important erminant is the concentration ratio of both these agents. In ver doses, the effects of propylene glycol are usually not a oblem. It has been suggested however that one reason for high incidence of hypotension at higher doses of Dilantin due to the additive effects of the propylene glycol with the lantin Because Dilantin causes venous irritation further lution from 50 mg /c c to 25 mg /c c with propylene glycol s been suggested. This is not advisable due to the increased ncentration of the solvent as compared to Dilantin Both e amount of Dilantin and the rate of administration is ucial to control the adverse effects of the two agents Rapid fusion of greater than 100 mg in a five minute period is not d sed. At lower than these doses hypotension should not be problem for most patients. However Zoneraich and other uthors have reported hypotension and sudden death even ith this regimen

The second point is the fact that a significant drug interac ion exists between isoniazid and Dilantin Isoniazid inhibits the hepatic metabolism of Dilantin Caution should be taken when these two agents are used together Numerous reports have appeared in the literature documenting Dilantin toxicity when patients have also been on isoniazid Reduced doses of Dilantin can be used to avoid this interaction The patient that was presented in Zoneraich and colleagues article was on maintenance isoniazid when she received Dilantin This inter action was probably not involved in this patient due to the rapidity of her death. However the concomitant use of Dilantin and isoniazid in *any* patient and its potential inter action should be noted and remembered

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REFERENCES

1 Zoneraich S., Zoneraich O., and Siegel J Sudden death following intravenous sodium diphenylhydantoin AM HEART J 91 375 1976
2. Louis, S Kutt, H and McDowell F The cardiocircu latory changes caused by intravenous Dilantin and its solvent AM HEART J 74 523 1967
3. Hansten P D Drug interactions 3rd edition p 140 Philadelphia 1975 Lea & Febiger
4 Kutt H et al Depression of parahydroxylation of diphenylhydantoin by antituberculosis chemotherapy Neurology 16 594 1966
5 Kutt H et al. Diphenylhydantoin intoxication atten dant to slow inactivation of isoniazid Neurology 20 687 1970
6. Kutt H et al. Diphenylhydantoin intoxication. A complication of isoniazid therapy Am Rev Respir Dis 101 377 1970
7 Murray F Outbreak of unexpected reactions among epileptics taking isoniazid Am Rev Respir Dis 86 729 1962.

Reply

To the Editor

Dr C S Kirman seemed to have ruled out both possible mechanisms of sudden death raised in her letter to the editor The dose of Dilantin was acceptable and the rate of adminis tration of the drug was slow enough. The drug interaction existing between isoniazid and Dilantin was probably not involved in this patient due to the rapidity of her death

One must however note that Dr Kirman failed to cite Hansten s conclusions (her reference 3) when she referred to his remarks on drug interaction Hansten felt that "Patients who are genetically slow inactivators of isoniazid may expe rience diphenylhydantoin toxicity when taking this drug concurrently with isoniazid If interaction occurs diphenylhy dantoin dosage should be reduced or discontinued until toxic manifestations subside and dosage adjusted to achieve a lower serum level " At the present time we are not aware of any method which could detect genetically "slow" inactiva tors of isoniazid

Dr Kirman avoided however to discuss the basic problem raised by the publication of this case such as the safe doses of antiarrhythmic agents. The electrophysiologists have been so far unable to provide us with the necessary information related to the selection of the drug of choice for suppressing certain arrhythmias The effective dose necessary to obtain a therapeutic blood level remains an unsolved problem Each patient responds differently to drugs. The clinician is unable to predict whether a patient will respond better to one drug or to another There is no common denominator for the indi vidual tailoring of the antiarrhythmic drug treatment Once we have decided to employ a specific antiarrhythmic drug the efficacy of the drug for controlling ventricular arrhythmias, for example could be determined to a certain point by using 24 hour ambulatory ECG monitoring and stress testing We are however unable to predict or to avoid in advance the toxic effects produced by a given drug Hence the basic

closer to the first heart sound It is possible that the known increase in blood volume that occurs with gestation favorably realigns the mitral valve complex by increasing left ventricular end diastolic volume and the long axis of the left ventricle which together with a reduction in peripheral vascular resistance diminishes the mitral regurgitation and subsequently the auscultatory findings of the MSC-LSM syndrome

As noted by Marcus and colleagues in their study the implications of these observations in our three patients have both diagnostic and therapeutic significance A history suggestive of the MSC-LSM syndrome should prompt a close review of previous medical records and provocative maneuvers such as squatting isometrics or phenylephrine infusion to elicit the murmurs at the bedside The patient should most certainly be re examined again postpartum

That bacterial endocarditis can occur in the MSC-LSM syndrome has been emphasized by Allen and associates.[8] If one believes that delivery is an indication for prophylactic antibiotics in patients with valvular heart disease the auscultatory variations that may occur in the MSC-LSM syndrome must be appreciated and must not deter recognition and proper management

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REFERENCES

1 Barlow J B and Pocock W A The [illegible] nonejection systolic clicks and associated mitral [illegible] murmurs Emphasis on the billowing mitral [illegible] syndrome AM HEART J 90 636, 1975.

2 Goldberg L M and Uhland H Heart [illegible] pregnancy A phonocardiographic study of the [illegible] ment progression and regression Dis. Chest [illegible] 1967

3 Braun K Yodfat, Y Weisskopf K and Sadowsky [illegible] The phonocardiogram of the innocent murmur of [illegible] nancy Israel Med J 17 253 1958

4 Gilston R J and McPhaul J J Jr [illegible] murmurs in pregnancy A reemphasis, Med. Ann. [illegible] 9 481 1955

5 Marcus, F I Ewy G A O Rourke R A Walsh, B [illegible] Bleick A C The effect of pregnancy on the [illegible] mitral and aortic regurgitation Circulation 41 [illegible] 1970

6 Bader M E., and Bader R A Cardiovascular hemodynamics in pregnancy and labor Clin Obstet Gynec 11 924 1968

7 Fontana M E Pence H L Leighton R F [illegible] Wooley C F The varying clinical spectrum of the systolic click-late systolic murmur A postural auscultatory phenomenon Circulation 41 807, 1970.

8 Allen H Harris A and Leatham A Significance [illegible] prognosis of an isolated late systolic murmur a 9 to [illegible] year follow up Br Heart J 36 525 1974

al History of Twenty five Years of American Cardiology 1974 Compiled and edited by [illegible] Grey Dimond M D rsda Maryland 1975 Accel, American College of Cardi Extended Learning Price $30 00

educational audiotape series Accel included a recent ation of selected aspects of the history of cardiology as ibuted by American cardiologists selected to relate some ir contributions to the development of cardiology These are valuable stories told by the cardiologists and cardiac ons of their own contributions This is a most interesting aluable set of tapes. Their value will increase with time of the contributors has already died unfortunately His voice is not only recorded for posterity but the tape ains his own ideas of his most important contributions to advancements in cardiology The others, although still g have recorded forever their voices and brief summaries eir contributions to cardiology The comments vary in th from two minutes to ten minutes

his is a most valuable collection of tapes. The editors of el were wise in recording them It is interesting to listen to contributors summarize their personal work Surely many have contributed much to cardiology Failure to ude them can be the only criticism of the tapes Regard it would be impossible to include every important tributing cardiologist in any tape series

ardiology advances yet we often fail to realize that people responsible in one way or another for these advancements listen to a few selected cardiologists not only brings to the ention of the listener the work of these cardiologists but wokes thought of the others not included in the series The tors of Accel are to be congratulated for this tape series rdiologists and all physicians and investigators in cardio scular science as well as young people contemplating reers in medicine medical science or science in general will t only want to listen to this set of tapes but would want to m a set

ypertens on A Pract cal Approach Edited by Marvin loser M D Boston 1975 Little Brown & Company 195 ages

This small paperback book edited by Dr Moser is intended r the practicing physician who treats people with hyperten on The presentation is not complicated by pathophysiologic iscussions. The role of renin the kidneys and pharmacologic ction of drugs are presented briefly to orient the physician oncerning the objectives and importance of therapy Two hapters are devoted specifically to management The lethora of monographs books and symposia and lectures on hypertension in recent months tend to overwhelm the doctor in practice but this book is short and concise Physicians will find it to contain a great deal of useful information that should assist them with the care of their patients. This is a good, practical, useful publication which should interest all physicians who treat patients with high blood pressure

Card ac Ultrasound Edited by Raymond Gramiak and Robert C Waag Saint Louis, 19 5 The C V Mosby Company 308 pages Price $34 50

This represents the proceedings of a symposium held in Boston on June 13 and 14 1974 on an extremely important and timely subject The contributors review the problem of echocardiography very well. The presentations include discussions of theory equipment, and technic as well as considerations of clinical applications Doppler echocardiography is also presented The recordings are good and the legends are clearly written The entire subject is well reviewed The material may appear a little old in such a rapidly developing field but surprisingly the presentations are timely and up to date This is a very good book which is highly recommended

Innovations in the Diagnosis and Management of Acute Myocardial Infarction Edited by Albert N Brest Leslie Wiener Edward K. Chung and Hratch Kasparian Philadelphia 1975 F A Davis Company 325 pages Price $28 00

This new book from the Cardiovascular Clinics Series like all previous ones, is very good and practical The contributors discuss pathology pathophysiology diagnosis and medical and surgical management The role of echocardiography coronary angiography and pacing are among the many aspects of management of acute myocardial infarction presented The title is misleading The word innovations may make the reader expect new and true innovations whereas he will find the discussions to consist of the usual approaches to myocardial infarction

Recent Advances in Studies on Cardiac Structure and Metabol sm vol 8 The Cardiac Sarcoplasm Edited by Paul Emile Roy M D., and Peter Harris M D Baltimore 1975 University Park Press 535 pages Price $39.50

Volume 8 of *Recent Advances in Studies on Cardiac Structure and Metabolism* contains papers presented at the 7th Annual Meeting of the International Study Group for Research in Cardiac Metabolism The presentations included aspects of comparative biology of cardiac and skeletal muscle protein synthesis, hypertrophy work and metabolism lysosome and other metabolic phenomena in cardiac muscle The many separate presentations are succinctly written and well illustrated The subject material is extremely important and represents fields of great research interest at present. This volume makes it possible for the readers to learn what transpired at the meeting This is a very good volume to include among the others in the series Cardiologists as well as biochemists will find the volume well worth studying

Recent Advances in Stud es of Cardiac Structure and Metabol sm vol 10 The Metabolism of Contraction Edited by Paul Emile Roy M D and George Rona M D Baltimore 1975 University Park Press 787 pages Price $39 50

This publication represents the proceedings of the Seventh Annual Meeting of the International Study Group for Research on Cardiac Metabolism. As with the past publications, this is another outstanding report The contributors represent the leaders in the field and the subjects discussed are not only important but well presented Among the many aspects discussed are cardiac lipid metabolism pharmacological action of commonly used drugs on the heart mechanical activity of cardiac muscle metabolic changes associated with myocardial ischemia cardiomyopathy and many others The many contributions found in this volume represent papers of tremendous value to anyone who is interested in the present state of interest and research in cardiac muscle metabolism This is a highly recommended book

principle adopted in daily practice remains *that all patients receiving the selected drug require continuous observation for adverse effects even if doses are within the currently recommended ranges*

There are situations when life threatening arrhythmias may cause serious symptoms or appear to have such an ominous prognosis that short term suppressive treatment is justified by sound clinical judgement

In such situations the medication should be administered under serious precautions including careful monitoring and availability of pacemakers

In our patient all these precautions including insertion of a pacemaker had been taken All means of resuscitation had proved in this particular case unsuccessful

The next question raised by this case and by other similar cases reported in the literature is the appropriateness of quick administration of antiarrhythmic drugs by the patient himself or by his family at any given location for prevention of sudden electrical death

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TAPVC vital statistics

To the Editor

I have read the paper by Georges Delisle and colleagues Total anomalous pulmonary venous connection Report of 93 autopsied cases with emphasis on diagnostic and surgical considerations that appeared in AMERICAN HEART JOURNAL vol 91 no 1 pp 99 122 January 1976. In this article stated that "This is the largest of series of TAPVC put to data This is not true From a collection of congenitally malformed hearts in 1973 Dr Lev and I re congenital anomalies of the pulmonary veins seen at Congenital Heart Disease Research and Training C Chicago Illinois There were 182 hearts with anomal pulmonary veins of which 138 hearts were of total anoma pulmonary venous drainage into systemic circulation T review was published in *Cardiovascular Clinics* 5(1) 1973 This to my knowledge is the largest series in well as of March 1976

The point I would like to make for future authors the literature carefully and include the previous work various people This may perhaps help in writing a p objective manner This I believe is basic to all aspects science An incomplete review and a misquote may erroneous ideas to a chance reader in this field

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Reply

To the Editor

Dr Bharati is right This was an unintentional oversight on our part Our thanks to Dr Bharati for referring us and other interested readers to her excellent paper with Dr Ma Lev

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American Heart Journal

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itorial

tral valve prolapse A plea for unanimity

athan Abrams M D
querque N M

ce the recognition in the early 1960s that lsystolic clicks and late systolic murmurs arise n the mitral valve apparatus a large body of rature has been generated by the many fasci ing aspects of this diverse clinical entity The ith African workers Reid and Barlow and ociates were among the first to emphasize it late systolic murmurs are the result of late tral insufficiency Early reports emphasized *lowing* or *ballooning* of the mitral valve rticularly the *posterior* leaflet and very ent publications also stress these descriptive ms Many series have underlined the relative nignity of the syndrome and in fact most ected individuals are probably asymptomatic ie group has estimated the prevalence as high 5 to 10 per cent of the population On the other ind disturbing reports of sudden death and e threatening ventricular arrhythmias have peared occurring perhaps in one per cent affected individuals

Symptoms if present include palpitations iest pain dyspnea and fatigue Midsystolic licks late systolic murmurs and holosystolic iurmurs can occur in various combinations and iolated clicks are quite common A peculiar and ommon feature is the extreme variability of hese findings in any given individual and the haracteristic changes in the timing of the click and murmur with postural alterations amyl nitrate vasopressors Valsalva maneuver hand grip etc Many symptomatic patients have inferolateral ST T changes on the resting ECG supraventricular and ventricular arrhythmias are frequent both at rest and after exercise and their presence correlates with a history of palpitations

Many names have been used to describe this syndrome (Table I) Most emphasize either the physical findings or a description of the mitral valve abnormality I would like to propose that only the term *mitral valve prolapse* or *mitral valve prolapse syndrome* (MVP) be used by future workers in an effort to clarify the confu sion in the literature and to emphasize this cardinal feature Angiographic studies have clear ly demonstrated that *prolapse* of the mitral valve is the *sine qua non* of the syndrome (with or without mitral insufficiency which is usually mild) Echocardiography has provided much additional information While it is not always easy to obtain a high quality echo demon strating prolapse it appears that an echo showing a midsystolic posterior motion of the mitral valve with or without anterior and poste rior leaflet separation or a hammock like defor mity of the mitral valve is seen in no other cardiac condition That prolapse can occur *without regurgitation* is clear this is seen in individuals with only a midsystolic click

Although many authors have stressed isolated posterior leaflet prolapse others have demonstrated anterior leaflet prolapse alone and more often prolapse of both leaflets

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Announcements

Advances in Clinical Medicine seminar

A seminar entitled *Advances in Clinical Medicine* will be held from September 27 to 30 1976 at the University of Texas Southwestern Medical School at Dallas Texas This seminar will provide the primary care practitioner an update on the significant recent advances in clinical medicine Emphasis will be placed on the common problems and practical solutions In addition to lectures and patient demonstrations, attendees will be provided a course syllabus and the opportunity to participate in teaching rounds and outpatient clinics at Parkland Memorial Hospital

Seminar chairmen are Drs Norman Kaplan Donald Seldin and Paul MacDonald The seminar is approved for Category I credit AMA 24 hours

For further information please contact Office of Continuing Education University of Texas Health Science Center 5323 Harry Hines Blvd Dallas Texas 75235 Telephone 214/688 2166 or 2167

International Conference on Cardiovascular System Dynamics

The International Conference on Cardiovascular System Dynamics will be held on October 3 through 7 1976 at the Hilton Hotel Philadelphia Pa Its theme will be *Significance of pulsations in the CV system* For further information regarding this conference please contact Dr Abraham Noordergraaf Department of Bioengineering D2 University of Pennsylvania Philadelphia Pa 19174 (for the U S A and Western Hemisphere) or Dr Jan Baan Department of Pediatrics University of Leiden The Netherlands (Europe and Eastern Hemisphere)

1977 Pediatric Cardiology Examination

The Sub Board of Pediatric Cardiology of the Board of Pediatrics will offer its next written examina[illegible] Friday, July 22 1977 The following criteria must be met [illegible] eligible to sit for the examination

1 Certification by the American Board of Pedia[illegible]

2. Two years of full time graduate training in an appr[illegible] pediatric cardiology program

3 Letters of recommendation from individuals [illegible] attest to the applicant s fellowship training

Candidates who achieve a qualifying score on the [illegible] examination will be eligible for the oral examination Th[illegible] portion of the examination will be held Thursday and F[illegible] November 3 and 4 1977 in New York City A candida[illegible] be successful on both the written and oral portions of th[illegible] examination in order to be certified

The registration period for the examination will exten[illegible] from August 1 1976 to November 30 1976 Req[illegible] applications received prior to the opening of registra[illegible] be held on file until August 1 1976 at which time appl[illegible] will be forwarded to those who have requested [illegible] examination fee is $300 00 and registration fee is $150 00 [illegible] $450 00

Please direct inquiries to American Board of Pedia[illegible] Children s Hospital 34th St & Civic Center Blvd Philadel[illegible]phia PA 19104 Telephone (215) 349 8500

posterior leaflet syndrome Minnesota multiphasic personality inventory profiles in symptomatic and asymptomatic groups Chest 66 6 19 4

O Rourke R A Crawford, M H Johnson A D et al Prolapsing mitral valve leaflet syndrome—University of California San Diego (Specialty conference) West J Med 122 217 19 5

Barlow J B Bosman C K Pocock W A and Marchand P Late systolic murmurs and non ejection (mid late) systolic clicks An analysis of 90 patients Br Heart J 30 203 1968

Hancock E W and Cohn K The syndrome associated with mid systolic click and late systolic murmur Am J Med 41 183 1966

Marshall C E and Shappell S D Sudden death and ballooning posterior leaflet syndrome Detailed anatomic and histochemical investigation Arch Pathol 98 134 1974

Jeresaty R M Mitral valve prolapse click syndrome Progr Cardio asc Dis 15 623 1973

Gooch A S Vicencio F Maranhao V and Goldberg H Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome Am J Cardiol 29 611 1972

Sloman G Wong M and Walker J Arrhythmias on exercise in patients with abnormalities of the posterior leaflet of the mitral valve AM HEART J 83 312 1972

Pocock W A and Barlow J B Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome Analysis of a further 130 patients with a late systolic murmur or non ejection systolic click Am J Med 51 731 1971

Popp R L, Brown O R Silverman J F and Harrison D C Echocardiographic abnormalities in the mitral valve prolapse syndrome Circulation 49 428 1974

Kerber R E Isaeff, D M and Hancock, E W Echocardiographic patterns in patients with the syndrome of systolic click and late systolic murmur N Engl J Med 284 691 1971

Dillon J C Haine C L Chang S and Feigenbaum H Use of echocardiography in patients with prolapsed mitral valve Circulation 43 503 1971

King, J F and Dunn M Mitral valve leaflets and systolic clicks (Letter to Ed) N Engl J Med 284 1379 1971

Gooch A S Maranhao V Scampardonis, G Cha S D and Yang S S Prolapse of both mitral and tricuspid leaflets in systolic murmur-click syndrome N Engl J Med 287 1218 1972

Ainsworth R P Hartmann A F Aker U and Schad N Tricuspid valve prolapse with late systolic tricuspid insufficiency Radiology 107 309 1973

21 Rizzon P Biasco G Brindicci, G and Mauro F Familial syndrome of mid systolic click and late systolic murmur Br Heart J 35 245 1973

22 Shell W E Walton J A Clifford M E and Willis, P W The familial occurrence of the syndrome of mid late systolic click and late systolic murmur Circulation 39 327 1969

23 Steinfeld L, Dimich I Rappaport, H and Baron M Late systolic murmur of rheumatic mitral insufficiency Am J Cardiol 35 397 1975

24 Steelman R B White R S Hill J C et al Mid systolic clicks in arteriosclerotic heart disease A new facet in the clinical syndrome of papillary muscle dysfunction Circulation 44 503 1971

25 Aranda J M Befeler B Lazzara R Embi, A, and Machado H Mitral valve prolapse in coronary artery disease Clinical hemodynamic and angiographic correlations Circulation 52 245 1975

26 Roberts W C Dangel J C and Bulkley B H Non rheumatic valvular cardiac disease A clinical pathologic survey of 27 different conditions causing valvular dysfunction in Likoff W Editor Cardiovasc Clin 5 339 1973

27 Bon Tempo C P Ronan J A de Leon A C and Twigg, H L Radiographic appearance of the thorax in systolic click late systolic murmur syndrome Am J Cardiol 36 27 1975

28 Salomon J Shah P and Heinle R A Thoracic skeletal abnormalities in idiopathic mitral valve prolapse Am J Cardiol 36 32 1975

29 Ehlers K H Engle M A Levin A R Grossman H and Fleming, R J Left ventricular abnormality with late mitral insufficiency and abnormal electrocardiogram, Am J Cardiol 26 333 1970

30 Liedtke A J Gault J H Leaman D M, and Blumenthal M S Geometry of left ventricular contraction in the systolic click syndrome Characterization of a segmental myocardial abnormality Circulation 47 27 1973

31 Gentzler R D Gault J H Liedtke A J McCann W D Mann R H and Hunter A S Congenital absence of the left circumflex artery in the systolic click syndrome Circulation 52 490 1975

32 Jeresaty R M Etiology of the mitral valve prolapse-click syndrome Am J Cardiol 36 110 1975

33 Nutter D O Wickliffe C Gilbert C A Moody C and King S B III The pathophysiology of idiopathic mitral valve prolapse Circulation 52 297 1975

34 LeWinter M M Hoffman J R Shell W E Karliner J S and O Rourke R A Phenylephrine induced atypical chest pain in patients with prolapsing mitral valve leaflets Am J Cardiol 34 12 1974

Table I Partial list of proposed names in the literature for Mitral Valve Prolapse Syndrome

Click-murmur syndrome
Click-late systolic murmur syndrome
Systolic click syndrome
Mitral click-murmur syndrome
Systolic click-late systolic murmur syndrome
Mid systolic click-late systolic murmur syndrome
The syndrome of mid systolic extra sound and late systolic murmur
Billowing mitral leaflet syndrome
Billowing posterior mitral valve leaflet syndrome
Prolapsing mitral valve leaflet syndrome
Ballooning posterior leaflet syndrome
Prolapsed mitral leaflet myocardiopathy
Mitral valve prolapse-click syndrome
Mitral valve prolapse syndrome
Floppy valve syndrome
Barlow s syndrome
The syndrome of apical systolic click late systolic murmur and abnormal T waves
The syndrome of mid systolic extra sound and late systolic murmur
The auscultatory-electrocardiographic syndrome

Milder degrees of mitral insufficiency are probably correlated with selective posterior leaflet prolapse[11] more severe mitral insufficiency is almost always seen when both the anterior and posterior leaflets are prolapsed and incompetent [3 11] Even the ability of the echocardiogram to identify selective leaflet prolapse has been questioned [15] Thus the common denominator of MVP does not justify the emphasis on *posterior* leaflet involvement Use of the terms billowing or ballooning is perhaps more aesthetic than accurate Some affected individuals also have prolapse of the tricuspid valve [19]

The etiology of mitral valve prolapse is varied Most cases are idiopathic, with a high incidence of familial involvement [8 14 21 2] The syndrome has been definitely found following documented rheumatic mitral insufficiency [14 3] While the association of midsystolic clicks and late systolic murmurs in coronary disease has been held to be coincidental by some [11] there is little doubt that MVP has been frequently documented in severe coronary atherosclerotic heart disease [24 5] Marfan s syndrome, either full blown or forme fruste has been suspected in some instances [11 14] Certainly the uniform finding of myxomatous degeneration and increase in the acid-mucopoly saccharide content of the mitral valve leaflets,[3 10 11 6] along with thin elongated chordae tendineae, suggests an underlying connective tissue defect There appears to be an increased incidence of minor skeletal abnormalities in affected individuals [12 7 8] MVP has also been associated with secundum ASD s and IHSS [7] Many groups have documented left ventricular contraction abnormalities in patients with MVP suggesting that a focal or generalized cardiomyopathy is a possible common link[12 ...] Others take exception to this view [3 33] In *all* of the above conditions, *the final common pathway is mitral valve prolapse*

One of the most vexing aspects of MVP is the presence of chest pain and ECG abnormalities There has been much speculation about the causes of these phenomena, and the most prevalent concept postulates an imbalance between myocardial oxygen supply and demand involving the papillary muscles and surrounding myocardium [11 34] The reason for this, and its documentation is obscure A recent study demonstrated congenital absence of the AV groove branch of the left circumflex artery in a high percentage of these patients [31] In any case MVP is clearly present in *all* such cases, and some suggest that the prolapse itself contributes to the relative ischemia by increasing tension in the papillary muscle [32]

Much is still unknown about various aspects of MVP The common utilization of the term mitral valve prolapse should result in decreased confusion in the literature and at the same time emphasize that diverse etiologies can result in prolapse It is the prolapse of either or both mitral leaflets into the left atrium with or without valve incompetence which results in the varied clinical sequelae Future research hopefully will better characterize the mechanisms resulting in prolapse and the effects of prolapse itself

REFERENCES

1 Reid J V Mid systolic clicks, S Afr Med J 35 ... 1961
2 Barlow J B Pocock W A Marchand P, and Denny M The significance of late systolic murmurs, Am Heart J 66 443 1963
3 Bittar N and Sosa J A The billowing mitral valve leaflet Circulation 38 763 1968
4 Jeresaty R M Ballooning of the mitral valve leaflet Angiographic study of 24 patients Radiology 100 ... 1971
5 Criley J M Lewis K B Humphries, J O and Ross R S Prolapse of the mitral valve Clinical and cine angiographic findings Br Heart J 28 488 1966.
6 Shappell S D Orr W and Gunn C G The balloon

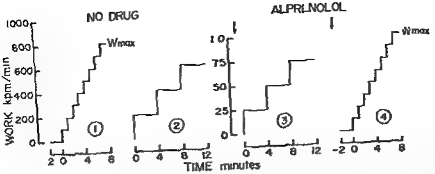

Fig 1 Relationship of rate of work (kpm/min) to duration of exercise in the different exercise tests performed before and after alprenolol (injections marked with arrow) W_m was determined during tests 1 and 4 (sprint) during tests 2 and 3 steady state" exercise was performed at levels of 0.25 0.50 and 0 75 W as determined in test 1 Further details in text

Table I Clinical data*

Patient	Age (yr)	Functional class (N Y H.A)	FEV/VC	Resting ECG (12 lead)	Per cent stenosis coronary angiography LAD (%)	LCX (%)	RCA (%)
1 J M	3[illegible]	[illegible]	2[illegible]/32	Nonspecific	100	90	90
2 A. T	64	3	—	Normal	[illegible]0	100	100
3 N M	43	3	[illegible]/44	Normal	> 80	[illegible]0	[illegible]0
4 J H	6[illegible]	2	[illegible]7/35	Normal			
5 C A	[illegible]	3	3[illegible]/36	Nonspecific	> [illegible]0	—	100
6 A F	[illegible]8	2	29/34	Nonspecific	> 80	[illegible]0	50
7 R. H	[illegible]	3	—	Nonspecific	100	> 50	> 80
8 R C	36	2	[illegible]/39	Nonspecific	—	90	—
9 R R	5[illegible]	4	2[illegible]/3[illegible]	Normal	100	[illegible]0	50

Abbreviations
NYHA New York Heart Association
FEV forced expiratory volume (L in 1 sec)
VC vital capacity (L)
LAD left anterior descending coronary artery
LCX, left circumflex coronary artery
RCA, right coronary artery
LV left ventricle
Nonspecific nonspecific ST and T wave changes

the study which had been approved by the Clinical Investigation Committee of the Royal Prince Alfred Hospital

Protocol The subject arrived in the laboratory at 8 30 A M the last meal had been taken the previous evening All medication had been suspended for the preceding 7 days except glyceryl trinitrate which was disallowed only on the day of the study A fine Teflon catheter (Dwellcath) was inserted percutaneously into the left brachial artery under local anesthesia and electrocardiogram (ECG) leads were attached (see Measurements) Exercise was performed on an electrically braked bicycle ergometer (Elema Schonader AB Stockholm Sweden) with the subject sitting upright The protocol consisted of four exercise tests (Fig 1) two before and two after the administration of alprenolol Before each test the patient cycled for 2 minutes without any load and at the end of each test he rested for at least 45 minutes before continuing

The *first test* determined maximum work capacity (W_m) by progressively increasing work load by 100 kpm per minute each minute The patient signalled the onset of chest pain but continued exercise until limited by the severity of symptoms (e g chest pain fatigue leg discomfort) W_m was defined as the maximum work

Effect of beta-adrenergic blockade with alprenolol on ST-segment depression and circulatory dynamics during exercise in patients with effort angina

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In evaluating the effects of antianginal agents the common practice is to employ a standardized exercise protocol before and after administration of the drug[1] In any given patient angina occurs at about the same time in the exercise schedule at an approximately constant value of one of the indices of myocardial oxygen consumption (MVo) e g changes in heart rate tension time index or double and triple products[1-3] A problem in the evaluation of the acute effects of drugs in patients with angina is that pain is a fairly quantal event in the standard exercise protocol Improvements produced by a drug can thus be expressed only in qualitative terms as the ability to continue the exercise for longer than before the drug or the ability to perform a more severe level of exercise It would be advantageous if with the use of objective criteria of ischemia the effect of a drug could be expressed by a shift in the entire workload—ischemic response curve

Myocardial ischemia occurs when oxygen demand exceeds supply and is usually associated with acute ST segment depression[4-11] Acute ST segment changes can now be recorded satisfactorily during exercise and the purpose of this study was to examine the effects of the beta adrenergic blocking drug *dl* aprenolol on ST depression and hemodynamic changes du[ring] exercise Two types of standardized exer[cise] protocols were employed (1) progressive pa[in] exercise where workload was increased rela[tively] rapidly until maximum work capacity (W[max]) w[as] reached (2) progressive steady state" exer[cise] where each of three levels of work was mai[ntained] for longer periods than during the pr[evious] ST segment changes during exercise were mo[ni]tored continuously and we measured car[diac] output during steady state exercise by the di[rect] Fick method without cardiac catheteriza[tion][1] and also the changes in blood pre[ssure] and heart rate

Methods

Subjects Nine male patients with a history [of] stable effort angina of at least 6 months dura[tion] known to be associated with acute ST segm[ent] depression were studied (Table I) In ea[ch] patients cineangiography had been perform[ed] and severe degrees of coronary artery obstruc[tion] demonstrated No patient had a history [of] myocardial infarction heart failure or lu[ng] disease or was receiving digitalis glycosides [All] patients had normal chest x rays Chest pain ha[d] been provoked previously in the laboratory un[der] conditions similar to those used in the pres[ent] study and all patients were familiar with the te[st] procedure In addition we also studied 13 appar[ently] normal healthy subjects, using the same protocol as during steady state exercise in the control period All patients and normal subjec[ts] had given their informed consent to participate

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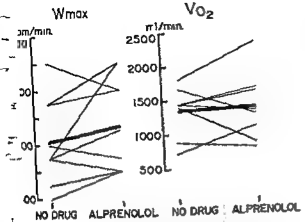


Fig. 3 Values of W_m (kpm /min left panel) and oxygen consumption ($\dot{V}_{O_2}$ mL/min right panel) in individual subjects (thin lines) obtained during control period before alprenolol (test 1 Fig 1) and after alprenolol (test 4 Fig 1) The average values have been joined by the thick lines. Oxygen consumption was determined during the last minute of each sprint.

and gas exchange During the first 2 5 minutes mixed expired gas was flushed continuously through the spirometer During the next minute arterial blood and mixed expired gas samples were collected simultaneously and immediately after ward the patient rebreathed a CO_2-O_2 mixture for a period of 12 seconds End tidal P_{CO_2} was measured continuously to determine the level at which no CO exchange occurred between mixed venous blood and the gas in the lungs Such an equilibrium is represented by a plateau in the end tidal Pco tracing and occurs after 6 to 10 seconds of rebreathing before the onset of recirculation Values for arterial and mixed venous CO content for use in the Fick equation were estimated from the arterial and mixed venous Pco using the CO_2 dissociation curve corrected for the effects of pH oxygen saturation and hemoglobin concentration For convenience a modification of the computer program of Godfrey was used to calculate cardiac output The time allowed for measuring cardiac output was adequate to reach a steady state as judged from studies in normal subjects where cardiac outputs measured at 3 6 and 9 minutes were all closely similar with a standard error of a single observation ± 6 per cent of the mean value (Bailey and Anderson unpublished data) Results obtained by the indirect Fick method during work correlate closely with results obtained by dye dilution However

Table II Cardiorespiratory changes under resting conditions and at W_m

	Resting		W_m	
	C	*A*	*C*	*A*
Work load (kpm /min)				
Mean			611	678
S E M			56 4	61.3
P			NS	
O consumption (mL/min)				
Mean			1,3₅7	1,399
S.E.M			138.5	187.9
P			NS	
Heart rate (b.p.m)				
Mean	71.2	0 1	139 2	121.9
S.E.M	3.1	2.84	8 3	7 49
P	NS		< 0 005	
Systolic pressure (mm Hg)				
Mean	120.9	113.8	153 7	149 4
S.E.M.	5 71	4.85	8.98	9.37
P	< 0 05		NS	
Double product†				
Mean	86 4	79 6	214	182 9
S E M.	6 07	4.98	17 25	16 71
P	NS		NS	
ST segment (mm)				
Mean	–0.23	–0 18	–3.3	–2.5
S E.M.	0 17	0.21	0.31	0 43
P	NS		< 0 05	
Arterial P_{O_2} (mm. Hg)				
Mean	81.5	81 0	104 7	94 1
S E.M	4.06	5.80	2 46	3.85
P	NS		< 0 005	

Resting values measured in recumbent position 5 minutes before test 1 (Fig. 1) C Control before giving alprenolol 1 A after alprenolol, NS not significant (P > 0 05)
†Systolic pressure × heart rate.

the method is not sufficiently accurate for measuring resting cardiac output

Plasma alprenolol levels were measured in six of the patients by the method of Ervik Two samples were obtained in each subject (1) between 60 and 90 minutes after the initial injection of 15 mg of alprenolol i.e after the third exercise test and (2) between 15 to 20 minutes after the booster dose of 5 mg of alprenolol i.e at the end of the fourth exercise test (Fig 1)

After each exercise test each patient provided a subjective evaluation of the severity of his symptoms, using a rating scale for chest pain leg fatigue[8] and perceived exertion as described in detail elsewhere

Mean values and standard errors of the mean were calculated with standard formulas Where

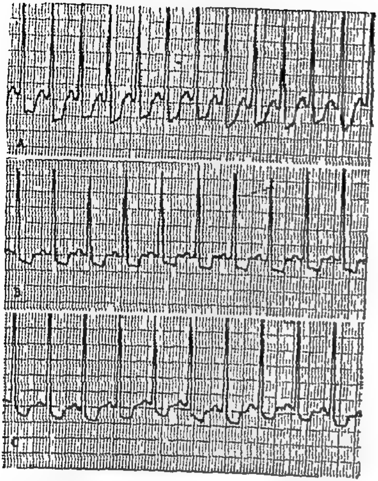


Fig 2 ECG tracings from patient J M all taken during sprint exercise *A* Before alprenolol at W_m 800 kpm heart rate 170/min ST depression 5 2 mm *B* After alprenolol at W 800 kpm heart rate 135/min ST depression 3 1 mm *C* Before alprenolol at submaximal sprint 600 kpm heart rate 135/mm (i e as in *B*) ST depression 3 0 mm

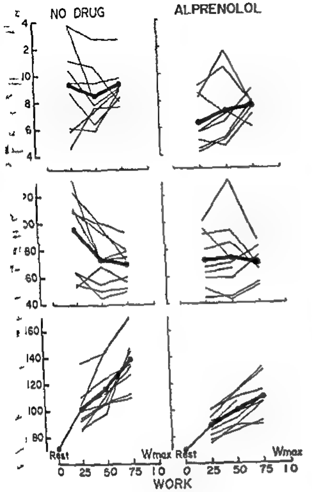
load completed by the patient If the symptoms became so severe that the patient was not able to complete a particular workload the duration of the period was rounded to the nearest half minute the W_m expressed to the nearest 50 kpm per minute During the *second test* period submaximal steady state exercise was performed by each patient at workloads of 0 25 0 50 and 0 75 of his own W The submaximal exercise period lasted 13 minutes, with each level of 4 minutes duration and no pause between work loads

Following the second rest period a standard dose of 15 mg of *dl* alprenolol (Aptin Hassle Laboratories of AB Astra Goteborg Sweden) was given intravenously over a period of 10 minutes The *third test* consisted of submaximal steady state exercise, with the same workloads in each patient as in the second test (Fig 1) In the *fourth test* W_m was again determined following previous administration of alprenolol and the method was identical to that used in the first test. To ensure adequate blood concentrations of drug each patient received a booster injection of 5 mg of alprenolol intravenously shortly before the fourth test In the present study placebo injections were not given in the third and fourth test periods in view of previous demonstrations of absence of placebo effects during acute studies of antianginal drugs[1, 15]

Measurements and calculations Heart rate and ST segment changes were recorded with an Avionics Exerstress Model 3000 Monitoring System with ST segment computer (Avionics California) A manubrial C5 bioplar ECG lead was commonly employed, with one electrode placed in the V_5 position and the other over the manubrium sterni (Fig 2) ST segment deviation was computed with reference to the baseline as established during the P Q interval (immediately following the P wave and just before the Q wave) measured at a point 70 ms past termination of the R wave downstroke (to minimize errors due to J point depression) and averaged over the preceding 15 beats All computed ST segment depressions were checked by direct measurement by one of the investigators

Systolic blood pressure was measured from the right arm with a blood pressure recorder with a microphone fitted to a standard cuff (Physiometrics Inc California) Double product was calculated as heart rate × systolic pressure Expired gas was collected in a 350 L Tissot spirometer (Collins Mass) and the patient breathed through a two way valve of low resistance and dead space Mixed expired gas from the spirometer was analyzed by means of an infrared capnograph for CO_2 (Godard Holland) and a paramagnetic oxygen analyzer (Servomex England) The results were recorded on a multichannel recorder (Devices England) Arterial P_{CO_2} and pH were measured by the Astrup technique with a Radiometer blood analyzer Arterial lactate was measured enzymatically[16]

Cardiac output was measured during each of the three submaximal steady state exercise levels by the indirect Fick CO_2 rebreathing method for determining the P_{CO_2} of mixed venous blood[1] At each workload a period of 2 5 minutes was allowed for the subject to reach a steady state of heart rate blood pressure, ventilation,



g 6 Relati n hip between steadv tate work (normalized terms of W) and cardiac output (L /min) stroke volume nL) and heart rate (beats min) before and after alpreno l

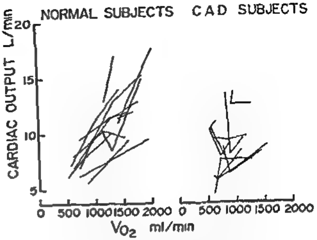


Fig 7 Relation hip between oxygen consumption ($\dot{V}o$ ml / min) and cardiac output (L /min) obtained in 13 n rmal and nine anginal subjects with coronary artery disease (CAD) during teady state exercise before alprenolol

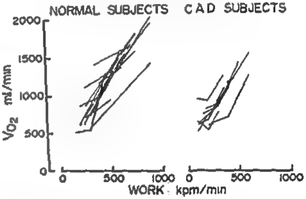


Fig 8 Relationship between work (kpm /m in) and oxyg n consumptic n ($\dot{V}o$ m l /min) in 13 normal and nine anginal subjects with coronary artery disease (CAD) during steady state exercise before alprenolol

antly smaller than during the control test at all workloads (Fig 5 $P < 0.01$) At W_m the mean difference in heart rates between the control period and after alprenolol was 17.3 ± 7.0 (S E M) beats per minute ($P < 0.01$) The attenuation of heart rate response tended to be less pronounced in patients who developed chest pain after alprenolol (in whom heart rate at W_m after alprenolol was 8 per cent below the rate during the control test) than in those who did not develop angina (in whom heart rate was 17 per cent below the control W_m value) Double product (systolic pressure × heart rate) was slightly reduced at W_m after alprenolol in 7 of the nine patients with the average reduction for the group 31.2 ± 16.4 units ($0.1 > P > 0.05$)

Steady state exercise After alprenolol the incidence of chest pain was smaller than before the drug at workloads of 0 50 W_m and 0 75 W_m (Table IV) At the latter level four out of eight patients considered that the exertion was subjectively less severe than before the drug No patient reported improvement in leg fatigue which was more severe in three and unaltered in five

During the control period (before alprenolol) the relationship between workload and degree of ST segment depression was again curvilinear (Fig 4 lower panels) In most patients the ST segment depression was greater than at rest even at the lowest workloads (0 25 W_m) For a

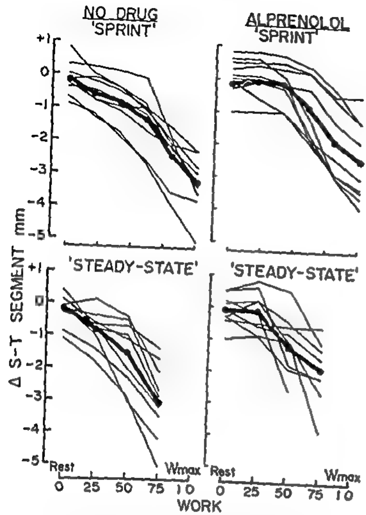


Fig 4 Relationship between work (normalized in terms of each subject W_m) and ST segment changes (mm) The top panels include the data before and after alprenolol during sprint exercise the bottom panels include data during steady state exercise The thin lines are the results in individual patients the thick lines and closed circles are the group means at each workload

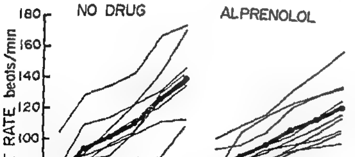


Fig 5 Relationship between work (normalized in terms of W_m) and heart rate (beats/min) during sprint exercise taken before and after alprenolol

appropriate, changes before and after alpre were analyzed within subjects by paired t te

Results

There were no complications from the proce dures in any subject or any side effects follow alprenolol Eight patients completed all fo exercise tests, but one patient did not comp the third level of submaximal steady sta exercise owing to the development of chest p (Table I, Patient 7)

Sprint exercise In this type of exercise W_m remained unaltered before and after alpreno (Fig 3) There were no significant changes in bod oxygen consumption or in respiratory m volume at W_{max} before and after alprenolol b arterial Po_2 was significantly lower after alp nolol than before the drug (Table II) Bef administration of alprenolol all patients de oped chest pain which set the limit to the performance at W_m After the drug four pati did not develop angina, though in these grea leg fatigue and perception of more severe e limited their performance (Table IV) to ess tially the same W_{ma} workloads as before the dr (Fig 3)

After alprenolol ST segment depression W_m was less pronounced than before the dr (mean difference 0 87 ± 0 37 [S E D] mm $P < 0\,05$) When ST segment depression plotted against workload (normalized as a pe centage of each patient s W_m), the relatio ship was curvilinear both before and after adm istration of alprenolol (Fig 4, top pane However before administration of the drug th ST segment depression of most patients w greater than at rest even at low workloads of 0 W_{ma} and 0 40 W_{ma} i e before onset of pa (Fig 3 top left) Administration of alprenolol h minimal effect on resting ST segment levels a at all workloads there was less pronounc ST segment depression than before the drug (Fi 4 top right) Moreover in most patien increasing the workload now had little effect o the degree of ST segment depression until wor loads of about 0 60 W_m Thus alprenol displaced the entire workload–ST segment r sponse curve to the right (Fig 4 top panels)

The resting heart rate was influenced on slightly by alprenolol (Table II) However, afte giving the drug the rise in heart rate was signif

nent at workloads of 0 25 W_m . Furthermore average ST segment depression at the two ier workloads during steady state exercise now closely similar to the average values erved during corresponding rates of work ing sprint exercise

lprenolol attenuated the exercise tachycardia ıll levels of exercise (Fig 6) and this accounted a substantial fraction of the lowering of the ıble product (Table III) Before alprenolol re was no significant relationship between the ınge in cardiac output and increased workload ł stroke volume tended to be higher at 0 25 where stroke volume was also reduced nificantly After alprenolol there was a work ated rise in cardiac output in five out of nine tients (Fig 6) Metabolic changes at low work ıd (0 25 W_m) were associated with significant luction in body oxygen consumption but at her rates of work oxygen consumption was not ered by alprenolol (Table III) An additional tabolic finding after alprenolol was that at 0 75 $_m$ the rise in arterial lactate concentration was ıaller than before the drug (Table III)

The lack of correlation between increased orkloads and rise in cardiac output in the ıtients with angina contrasted with the sponses of a group of subjects with normal ırdiac function studied by the same method over similar range of body oxygen consumption ig 7) However the relationship between body ygen consumption and workload was similar in ie normal subjects and in the patients with ngina (Fig 8)

Plasma alprenolol levels Alprenolol concen rations taken between 60 and 90 minutes after ıjecting 15 mg of alprenolol intravenously aver ged 50 6 ± 15 0 ng per milliliter of plasma hose taken 15 minutes after an additional ooster of 5 mg intravenously averaged 112 2 ± 1 1 ng per milliliter

Discussion

The present findings in patients with severe angina have demonstrated a curvilinear relation ship between workload and ST segment depres sion when the former is normalized in terms of W_m for each patient After alprenolol there is a shift to the right in the stimulus response curve compared with that obtained under control conditions. This extends earlier observations (e g Gianelly and associates[2]) and shows that over the whole range of workloads there is less ST segment depression after beta adrenergic blockade than under control conditions The shift to the right after alprenolol occurs during both "sprint and steady state types of exercise With each type of exercise the threshold for producing increased ST segment depression (in relation to resting) has increased after beta blockade and significant ST depression (in rela tion to resting) during exercise now requires higher workloads than before blockade After alprenolol more work could be performed without developing ST segment depression than under control conditions and the highest workloads studied have been associated with diminished ST depression These findings correlate with the elevation of angina threshold in most patients at the lower workloads and the reduced incidence of disabling pain at the higher rates of work They thus support the well known observation that in the present clinical setting acute ST segment depression serves as an index of myocardial ischemia [1] The present method of determining a stimulus response curve relating work to

Table IV Subjective evaluation of exercise after alprenolol

	Less severe	*More severe*	*Unaltered*
Chest pain			
0 5 W_m ("steady state" exercise)	4 (1 no pain)	2	3 (all no pain)
0 75 W_m ("steady state" exercise)	6 (2 no pain)	1	1 (no pain)
W ("sprint" exercise)	4 (all no pain)	3	2
Leg fatigue			
0.5 W_m ("steady state" exercise)	0	4	5 (3 no fatigue)
0 75 W_m ("steady state" exercise)	0	3	5 (3 no fatigue)
W_m ("sprint" exercise)	0	9	0
Perceived exertion			
0 5 W_m ("steady state" exercise)	4	3	2
0 75 W_m ("steady state" exercise)	4	2	2
W_m ("sprint" exercise)	0	9	0

Figures indicate number of patients. One patient did not complete 0 75 W after alprenolol due to chest pain.

Table III Steady state' exercise

Work level	0.25 W_m (9 subjects)		0.50 W_m		0.75 W_m (8 subjects)	
	C	A	C	A	C	A
Heart rate (b p m)						
Mean	101.8	88.4	117.0	100.0	138.0	110.0
SEM	3.14	3.29	5.37	4.03	5.94	[illegible]
P	< 0.005		< 0.005		< 0.001	
Systolic pressure (mm Hg)						
Mean	146.2	130.0	150.2	141.2	162.7	[illegible]
SEM	5.68	6.84	7.37	9.28	11.1[illegible]	[illegible]
P	< 0.005		NS		NS	
Double product						
Mean	135.7	112.5	172.0	139.1	217.7	[illegible]
SEM	8.05	6.66	12.32	11.81	15.7	13.5
P	< 0.001		< 0.02		< 0.005	
Cardiac output (L/min)						
Mean	9.27	6.36	8.44	7.2	9.32	[illegible]
SEM	1.16	0.64	0.75	0.83	0.5[illegible]	0.31
P	0.005		0.05		0.025	
Stroke volume (ml)						
Mean	96.0	72.3	73.4	73.7	69.9	69.5
SEM	10.67	7.18	7.53	9.6[illegible]	5.51	[illegible]
P	< 0.02		NS		NS	
O_2 consumption (ml)						
Mean	686.0	582.8	814.0	8[illegible]7.0	114[illegible]	1141
SEM	47.4	45.4	[illegible]9.1	42.9	9[illegible].3	[illegible]
P	0.005		NS		NS	
ST segment (mm)						
Mean	–0.82	–0.14	–1.54	–1.21	–3.08	–1.9[illegible]
SEM	0.19	0.22	0.36	0.41	0.42	0.3
P	< 0.005		NS		< 0.005	
Arterial P_{O_2} (mm Hg)						
Mean	94.3	90.7	96.3	95.9	99.2	94.1
SEM	4.2	4.3	3.1	3.9	2.5	3.6
P	NS		NS		NS	
Arterial P_{CO_2}						
Mean	36.6	34.6	33.7	34.7	34.1	33.9
SEM	1.8	2.4	2.0	2.1	1.6	2.3
P	NS		NS		NS	
Lactate (mM/L)						
Mean					3.38	2.[illegible]
SEM					0.3	0.[illegible]
P					0.05	

C Control before giving alprenolol A after alprenolol In one subject ST segment depression was markedly enhanced after alprenolol and he did not perform 0.75 W

given rate of work ST segment depression was greater during the prolonged steady state exercise than at the same rate of work in the more rapidly progressive sprint during the control period (Fig 4) For example the average ST segment depression at 0.75 W_m was 3.1 mm during steady state exercise compared with 2.1 mm during sprint ' Indeed the ST segment depression at 0.75 W_m, during steady state exercise was similar in most subjects to that observed at W_m following the sprint During control steady state exercise performed at 0.75 W_m most patients complained of pain before receiving the drug suggesting that this workload was not far from their upper performance limit for sustained exertion After alprenolol the entire workload-ST segment depression curve was shifted to the right as during sprint exercise (Fig 4 lower panels) with no longer consistent changes from resting in the level of the ST

ent at workloads of 0 25 W_{m} Furthermore, average ST segment depression at the two er workloads during steady state exercise now closely similar to the average values ned during corresponding rates of work ng sprint exercise

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Leg fatigue			
0 5 W_{m} (steady state" exercise)	0	4	[illegible] (3 no fatigue)
0 75 W_{m} (steady-state exercise)	0	3	5 (3 no fatigue)
W_{max} (sprint" exercise)	[illegible]	9	0
Perceived exertion			
0 5 W_{m} (steady state" exercise)	4	3	2
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ST segment depression has the advantage that by examining the ST segment responses elicited by a whole range of workloads it facilitates recognition of small ischemic changes at low workloads, which would be considered insignificant were the exercise to be performed at a single workload It appears that the work threshold for eliciting early myocardial ischemic changes is less than the work required to develop angina

Alterations in heart rate are an important determinant of myocardial oxygen consumption with other factors including afterload contractility, and heart size each playing a significant though smaller role Alprenolol attenuates the exercise tachycardia during both sprint and 'steady state' work and this appears to be the major mechanism whereby the drug lowers myocardial oxygen demand in the present study It has been previously shown that at relatively high workloads ventricular volume increases after beta blockade with propranolol thereby tending to increase myocardial oxygen demand In contrast to the latter drug alprenolol has no effect on resting heart rate (cf Ablad et al) so that resting ventricular volume would be less likely to alter We have not determined the effects on ventricular volume during the different work loads in the present study

Under control conditions (tests 1 and 2 Fig 1) steady state exercise at a given rate of work elicits more marked ST segment depression than a sprint in the same patient at the same rate of work After alprenolol the differences between the two types of work have been much less striking The question arises why prolonging the exercise at a given rate of work should aggravate myocardial ischemia before giving alprenolol but not after giving the drug Under control conditions exercise tachycardia has tended to be greater during steady state exercise compared with sprint at a given workload and this difference is no longer present after alprenolol (Figs 5 and 6) It is possible that under control conditions circulating adrenal catecholamines contribute more to the enhancement of body oxygen consumption and myocardial oxygen demand during 'steady state exercise than during sprint at the same rate of work and that this effect is antagonized by alprenolol In favor of this suggestion is the lowering of body oxygen consumption after alprenolol during steady state effort at 0 25 W_m and the reduced rise in lactate production at 0 75 W_{max} Both these effects could be explained by the blocking action of alprenolol on $\beta 2$ adrenoreceptors Alprenolol is a nonselective beta blocking drug which blocks both the cardiac $\beta 1$ and the peripheral $\beta 2$ adrenoreceptors

The absence of significant correlation between increased workload and rise in cardiac output in the patients with angina has been an unexpected finding It contrasts with the highly significant association between the above variables in a group of subjects with normal hearts The reasons for the fixed cardiac output during exercise in the anginal subjects are not clear in view of absence of any evidence for the development of cardiac failure (see below) The data in Figs 6 and suggest that during steady state exercise at 0.25 W_m the cardiac output in anginal patients may have been inappropriately high Such an effect could be mediated through reflexes arising from cardiac mechanoreceptors during the early development of myocardial ischemia During steady state exercise the effects of alprenolol have been most pronounced on the relatively high cardiac output at low workloads both by attenuating the heart rate response and by reducing stroke volume (Fig 6) When viewed in conjunction with its metabolic effects on oxygen consumption the drug is probably responsible for a substantial reduction in cardiac oxygen demand

During steady state exercise there has been no suggestion of development of cardiac failure either before or after alprenolol Indeed after alprenolol perception of effort at 0 75 W was either less severe or unaltered in six out of eight patients and there was no significant change in arterial P_O By contrast the findings obtained after alprenolol during sprint exercise performed at W are consistent with the development of mild left ventricular failure in view of the general complaint of more marked perception of effort and reduction in arterial P_O the latter suggests pulmonary congestion and ventilation perfusion inequalities The tendency to complain of greater leg fatigue after alprenolol (Table II implies less satisfactory perfusion of active muscles possibly related to the lower cardiac output during exercise produced by the drug In these patients with severe coronary disease although exercise performed after giving alprenolol evokes less aggravation of myocardial

emia, the cardiac pumping capacity remains ted and cannot be greatly extended in the nce of sympathetic support to the heart he finding of unaltered W_{m} after alprenolol rs from several previous studies which have orted that W_{m} increases after beta blockade r giving oral doses of alprenolol which duces blood concentrations of drug similar to se of the present study [8] In the latter dies the effect of the drug on work capacity has n assessed in terms of altered duration for eloping symptoms during exercise performed a single load [3] or in terms of workloads ched during progressive "steady state" type rcise [28] as during submaximal exercise in the sent study In none of these investigations was truly limiting value of W_{m} determined as ring the "sprint" exercise of the present study also seems likely that the steady state value 0 75 W_{m} (with W_{m} determined during progressive "sprint") has brought most of the tients closer to their upper performance limit st stained effort than in previously used proto ls for submaximal forms of exercise

In conclusion derivation of full workload–ST pression response curves enhances the ability to tect early myocardial ischemia during exercise patients with severe coronary artery disease esults with alprenolol show displacement of the ture stimulus response curve with diminished chemic changes occurring at all workloads Use f the indirect Fick method for measuring cardiac utput is a valuable minimally invasive method quantitative exercise testing and in the clinical nalysis of the actions of anti anginal drugs The methods of deriving workload–ST depression and ardiac output response curves may have applica ions as sensitive tests for observing changes in myocardial ischemia and cardiac pumping capac ty before and after coronary artery surgery

Summary

1 Nine subjects with severe coronary artery disease were studied during graded "sprint" and "steady state" exercise before and after intra venous administration of the beta receptor antag onist alprenolol During sprint workload was increased every minute until maximum work capacity (W_{m}) was reached Steady state exercise was performed at work rates of 0 25 0 50 and 0 75 of each subject's sprint W_{m} Variables measured included ST segment depression changes in heart rate blood pressure respiratory gas exchange and arterial blood composition Cardiac output (indirect Fick) was measured during steady state exercise

2 Alprenolol did not alter W_{m} during sprint but reduced the incidence of angina in both types of exercise After the drug work capacity was limited by symptoms and signs suggestive of mild left ventricular failure

3 The relationship between workload (normal ized in terms of W_{m}) and ST segment depression was curvilinear Under control conditions a given rate of work during steady state exercise was associated with more marked ST segment depres sion than during "sprint" Alprenolol displaced the work–ST depression curve to the right in each type of exercise now a given rate of work produced similar ST depression during steady state and sprint exercise

4 Alprenolol attenuated the exercise tachy cardia during both types of exercise Cardiac output was lower in "steady state" exercise after the drug than under control conditions Meta bolic effects included significant reduction in body oxygen consumption after alprenolol at 0 25 W_{m} and diminished arterial lactate at 0 75 W_{m} The beneficial effects of the drug thus appeared to involve not only cardiac but peripheral effects on beta receptors

5 Before alprenolol cardiac output was rela tively fixed at all workloads but after the drug there was a work related rise in output in five out of nine subjects Comparison with data in normal subjects suggested that in anginal subjects cardiac output at low steady state workloads was inappropriately high

We would like to thank Dr Brian Clarke for assistance in connection with the computer program Mr Philip Sammel for carrying out the lactate determinations, and Dr M Ervik of Hassle Laboratories of AB Astra Coteborg Sweden for performing plasma alprenolol levels. Astra Chemicals Pty Ltd. North Ryde Australia kindly supplied the alprenolol (Aptin)

References

1 Redwood, D R., Rosing, D R. Goldstein R. E Beiser C [illegible] and Epstein S E Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris, Circulation 43 618 1971

2 Goldstein R E., Beiser G D., Redwood D R Rosing D R., Stampfer M and Epstein S E Clinical and circulatory effects of isosorbide dinitrate (Isordil) during exercise in patients with angina pectoris, Circulation 49 40 (Suppl. III) 92, 1969

3 Sarnoff S J Braunwald, E., Welch G H Case R B

ST segment depression has the advantage that by examining the ST segment responses elicited by a whole range of workloads it facilitates recognition of small ischemic changes at low workloads, which would be considered insignificant were the exercise to be performed at a single workload It appears that the work threshold for eliciting early myocardial ischemic changes is less than the work required to develop angina

Alterations in heart rate are an important determinant of myocardial oxygen consumption with other factors including afterload contractility, and heart size each playing a significant though smaller role Alprenolol attenuates the exercise tachycardia during both sprint and steady state work and this appears to be the major mechanism whereby the drug lowers myocardial oxygen demand in the present study It has been previously shown that at relatively high workloads ventricular volume increases after beta blockade with propranolol thereby tending to increase myocardial oxygen demand In contrast to the latter drug alprenolol has no effect on resting heart rate (cf Ablad et al) so that resting ventricular volume would be less likely to alter We have not determined the effects on ventricular volume during the different workloads in the present study

Under control conditions (tests 1 and 2 Fig 1) steady state exercise at a given rate of work elicits more marked ST segment depression than a sprint in the same patient at the same rate of work After alprenolol the differences between the two types of work have been much less striking The question arises why prolonging the exercise at a given rate of work should aggravate myocardial ischemia before giving alprenolol but not after giving the drug Under control conditions exercise tachycardia has tended to be greater during steady state exercise compared with sprint at a given workload and this difference is no longer present after alprenolol (Figs 5 and 6) It is possible that under control conditions circulating adrenal catecholamines contribute more to the enhancement of body oxygen consumption and myocardial oxygen demand during steady state exercise than during sprint at the same rate of work and that this effect is antagonized by alprenolol In favor of this suggestion is the lowering of body oxygen consumption after alprenolol during steady state effort at 0 25 W_m and the reduced rise in lactate production at 0 75 W_m Both these effects could be explained by the blocking action of alprenolol on $\beta 2$ adrenoreceptors Alprenolol is a nonselective beta blocking drug which blocks both the cardiac $\beta 1$ and the peripheral $\beta 2$ adrenoreceptors

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...tatistical analysis of the different factors which could ...fect postextrasystolic potentiation in the human heart

...igo A Palmero M D
...omas E Caeiro M D
...udad de Córdoba Argentina

...he discovery of postextrasystolic potentiation ...as been attributed to Lagendorff[1] in 1895

Many studies performed at that time[2] deter...ined several basic concepts prematurity and ...otentiation prolonged duration of the potentia...on and the fact that two premature beats ...otentiate more than one

Wiggers[4,5] studied the mechanical effect of ...remature beats but did not concentrate on ...ostextrasystolic potentiation

In 1941 Cattell and Gold[6] studied this phenom...non in the cat papillary muscle Other works on ...his subject were later published by Hoffman and ...ssociates and Lendrum and associates All ...hese papers conclusively demonstrated that ...postextrasystolic potentiation means increase in ...ardiac contractility regardless of changes in pre ...and afterload

A comprehensive historical review of the subject was written by Cranefield[9] Recently Beck and associates tried to explain different behaviors of aortic and left ventricular pressures after a premature beat in the intact human heart

The purpose of our work was to investigate the changes in left ventricular systolic pressure end diastolic pressure and max dp/dt in the human heart after a premature beat and to make a statistical analysis of the different factors which may condition these changes

Methods

Twenty subjects aged 20 to 65 years who underwent diagnostic cardiac catheterization participated in this study Six patients had cardiomyopathies of various etiologies five had essential hypertension four had aortic or discrete subaortic stenosis and five had normal cardiovascular function All diagnosis were based on results of complete right and left cardiac catheterization The five subjects with a normal heart were studied because of the presence of functional murmurs They all received 50 mg of meperidine and 25 mg of promethazine hydrochloride an hour before the pressure recordings were made

Left ventricular pressure was recorded before angiography with the use of fluid filled catheters an EMT 35 Elema Schonander transducer and a multichannel Mingograph 34 recorder Special care was taken to improve the frequency response of the pressure recording system The system was thoroughly flushed to remove air bubbles and a special dumping needle was used for critical dumping of pressure recordings

The selected ventricular premature contractions occurred either spontaneously or after induction by mechanical or electrical stimulation In few cases a bipolar catheter was introduced in the right ventricle and single supraliminal stimuli were randomly delivered while pressures were being recorded in the left ventricle The mechanical stimulation was provoked either with a catheter in the right ventricle or by performing short and quick movements with the catheter placed in the left ventricle trying to avoid pressure curve distortions Atrial premature beats and all the ventricular premature beats with artifacts were not included in this study and only single ventricular premature beats occurring in a basal condition were considered The requirements for basal conditions were four regular sinus beats before and after the prematurity

The paper speed was 25 mm per second Peak systolic and end diastolic left ventricular pres...

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Stainsby W N and Macruz R Hemodyamic determinants of oxygen consumption of the heart with special reference to the tension time index Am J Physiol 192 148 1958

4 Katz L N and Feinberg [illegible] The relation of cardiac effort to myocardial oxygen consumption and coronary flow Circ Res [illegible] 636 1958

5 Monroe R G Myocardial oxygen consumption during ventricular contraction and relaxation Circ Res 14 294 1964

6 Robinson [illegible] F Relation of heart rate and systolic blood pressure to the onset of the pain in angina pectoris Circulation 35 1073 1967

7 Robinson [illegible] F Mode of action of nitroglycerin in angina pectoris Correlation between hemodynamic effects during exercise and prevention of pain Br Heart J 30 295 1968

8 Nyberg G Methodological aspects on drug testing in angina pectoris M D Thesis University of Goteborg Sweden 1973

9 Herman M V Elliott W C and Gorlin R An electrocardiographic and metabolic study of zonal myocardial ischemia in coronary heart disease Circulation 35 834 1967

10 Detry J M R Piette F and Brasseur L A Hemodynamic determinants of exercise ST segment depression in coronary patients Circulation 42 593 1970

11 Detry J M R and Bruce R A Effect of physical training on exertional ST segment depression in coronary heart disease Circulation 44 390 1971

12 Douglas C G and Haldane J Q The regulation of the general circulation rate in man J Physiol 56 69 1922

13 Jones N L Campbell E J M McHardy G J R Higgs B E and Clode M The estimation of carbon dioxide pressure of mixed venous blood during exercise Clin Sci 31 311 1967

14 Higgs [illegible] E Clode M McHardy G J [illegible] Jones N L and Campbell E J M Changes in ventilation gas exchange and circulation during exercise in normal subjects Clin Sci 32 329 1967

15 Wilson A G Brooke O G Lloyd H J and Robinson B F Mechanism of action of β adrenergic receptor blocking agents in agina pectoris Br Med J 4 399 1969

16 Hohorst [illegible] J *In* Bergmeyer H U editor Methods of enzymatic analysis New York 1963 Academic Press Inc p 266

17 McHardy G J R The relationship between the differences in pressure and content of carbon dioxide in arterial and venous blood Clin Sci 32 311 1967

18 Godfrey, S Manipulation of the indirect Fick [illegible] by a digital computer program for the cal[illegible] exercise physiology results Respiration 27 313 [illegible]

19 Ervik M Gas chromatographic determination of [illegible] secondary amine alprenolol as its trifluoroacetyl de[illegible] tive at nanogram level in biological fluids, Acta Pha[illegible] Seuc 6 393 1969

20 Borg G Perceived exertion at physical exercise [illegible] Swedish) Lakartion 67 4548 1970

21 Snedecor G W and Cochran W G Statistical [illegible] ods ed [illegible] Ames Iowa 1967 The Iowa State U[illegible] Press.

22. Gianelly R E Treister [illegible] L and Harrison D C [illegible] effect of propranolol on exercise induced ischemi[illegible] depression Am J Cardiol. 24 161 1969

23. Sonnenblick E H Ross, J Jr and Braunwa[illegible] Oxygen consumption of the heart Am J Car[illegible] 22 328 1968

24 Braunwald, E Ross J Jr and Sonnenbli[illegible] E H Mechanism of contraction of normal and failing hear[illegible] Engl J Med 277 962 1967

25 Åblad B Brogard M and Ek L Pharmacol[illegible] properties of H56/28—a β adrenergic receptor antag[illegible] Acta Pharmacol Toxicol 25 (Suppl. 2) 9 196[illegible]

26 Zeidifard [illegible] Non invasive methods of measur[illegible] cardiac output during exercise Ph D Thesis, Univer[illegible] of London 1974

27 Malliani A Schwartz P J and Zanchetti, [illegible] sympathetic reflex elicited by experimental cor[illegible] occlusion Am J Physiol 217 703 1969

28 Sealey B J Liljedal, J Nyberg G, and Åblad, B. Acute effects of oral alprenolol on exercise toleran[illegible] patients with angina pectoris A dose-response study Br Heart J 33 481 1971

29 Heatherington D J Comerford M [illegible] Nyberg G [illegible] Besterman [illegible] M M Comparison of two adren[illegible] receptor blocking agents alprenolol and propranol[illegible] treatment of angina pectoris Br Heart J 35 3[illegible]

30 Åblad [illegible] Johnsson G Norrby A and Solvell [illegible] Potency and time effect relation hip in man of pro[illegible] nolol and H56/28—comparative studies after oral ad[illegible] istration Acta Pharmacol Toxicol 25(Suppl [illegible] 1967

31 Sealey [illegible] J Liljedal J Åblad [illegible] and Nyberg G Th[illegible] effects of intravenous alprenolol on exercise tolera[illegible] patients with angina pectoris Pharmacol Clin 2 [illegible] 1969

32 Keyriläinen O Nyberg, G and Uusitalo A Effects [illegible] alprenolol and isosorbide dinitrate in angina pectoris Acta Med Scand 193 281 1973

Index 3			Index 4		
r	b	P	r	b	P
−0 34	−0 12	+ +	0 34	7 6	+ +
0 33	0 07	+ +	−0 56	−7 99	+ +
0 16	0 0?	NS	−0 36	−3 96	+ +
0 08	0 01	NS	−0 15	−1 40	+ +
−0 ?1	−0 16	+	0 ?2	10 8	+
0 44	0 8	+ +	−0 64	− 5 97	+ +
0 ?0	0 11	+	−0 44	−10 5?	+ +
0 08	0 01	NS	−0 8	−4 20	+
−0 07	−0 11	NS	0 18	18 18	NS
−0 ?3	−0 ??	+	−0 25	−15 03	+
0 11	−0 11	NS	−0 13	−8 88	NS
0 11	0 09	NS	−0 10	−5 35	

l) Index 4 EX R/R R The R R and EX R ıtervals have been included in each one of our ıdices in the order that the heart rate exerts its ıfluence

Correlations of each previously mentioned nterval or index against left ventricular systolic ressure left ventricular end diastolic pressure ınd max dp/dt of four postextrasystolic beats vere calculated Table I shows correlations with 102 ventricular premature contractions belonging ■ 20 patients and Table II the same correlations with 22 ventricular premature contractions corresponding to a single patient (reserpinized hypertensive) Table III shows data from four patients who had ventricular premature beats from right and left ventricles The statistical work was performed with a 1130 IBM digital computer

Results

Table I shows correlations between per cent changes in max dp/dt left ventricular systolic and end diastolic pressures and different intervals and indices in four postextrasystolic beats of 102 premature beats corresponding to 20 patients

Table II shows the same correlations of 22 extrasystoles corresponding to a single patient

Index 1 which represents the coupling interval and Index 4 which represents the postextrasys tolic pause have variable statistical significance when considering the correlations against left ventricular systolic pressure and max dp/dt Therefore we prefer to concentrate on the behavior of Index 2 which includes both intervals and gives a better statistical significance Index 3 is very similar to Index ■ For the above mentioned reasons from now on we will consider the behavior of the different mentioned parameters as a function of Index 2

First postextrasystolic beat The regression of left ventricular systolic pressure and Index 2 (Figs 2 and 3) shows a negative slope and a poor correlation (R 0 28 p, 0 05) It means that the shorter the R EX interval and the longer the postextrasystolic pause (Index 2 smaller) the higher the left ventricular systolic pressure will be and *vice versa*

The correlation between max dp/dt and Index 2 is much better than the previous one (R 0 51 p 0 01 in Table I R 0 94 p 0 001 in Table II) Here again the regression line has a negative slope

Left ventricular end diastolic pressure and Index 2 gives a negative regression in Table I However the correlation is very poor and a great *dispersion of data is shown in Fig 3 Few patients* and the patient of Table II show a regression line with a positive slope different from that observed in Table I

Second postextrasystolic beat The second postextrasystolic beat regression lines of left ventricular systolic pressure and max dp/dt against Index 2 show inverted slopes when compared with those of the first postextrasystolic beat (Table I Fig 2) This slope inversion phenomenon occur in a vast majority of the patients studied The slope inversion ■ not observed in the left ventricular end diastolic pressure which usually returns to control values in the second postextrasystolic beat (Fig 2)

Third and fourth postextrasystolic beats The *regression of left* ventricular systolic pressure and max dp/dt against Index 2 continue with the same sign observed in the second beat but with a less accentuated slope (Table I Fig 2)

Left ventricular end diastolic pressure correlations against left *ventricular systolic pressure* and max dp/dt The two correlations made to investigate the influence of changes in left ventricular end diastolic pressure over changes in left ventricular systolic pressure and max dp/dt failed to show statistical significance

Table I Correlations between per cent changes in left ventricular systolic pressure max dp/dt and left ventricular end diastolic pressure and Index 2 of 102 ventricular premature beats corresponding to ... subjects*

Post extra systolic beats	R EX r	R EX b	R EX P	R R r	R R b	R R P	EX R r	EX R b	EX R P	Index 1 r	Index 1 b	Index 1 P	Index 2 r	Index 2 b
Left ventricular systolic pressure														
1	−0.08	−0.001	NS	0.13	0.005	NS	0.32	0.009	+	0.04	0.02	NS	−0.25	−0.2
2	−0.06	−0.003	NS	0.25	0.006	NS	−0.45	−0.008	++	−0.24	−0.007	+	0.46	0.3
3	−0.07	−0.002	NS	0.14	0.002	NS	−0.29	−0.004	+	−0.13	−0.03	NS	0.25	0.11
4	−0.04	−0.001	NS	0.03	0.000	NS	−0.15	−0.001	NS	−0.04	−0.008	NS	0.09	0.0
Max dp/dt														
1	−0.16	−0.02	NS	0.06	0.005	NS	0.21	0.01	+	−0.23	−0.25	+	−0.51	1.6
2	−0.06	−0.007	NS	0.39	0.02	++	−0.46	−0.02	++	−0.39	−0.36	++	0.41	0.3
3	−0.09	−0.006	NS	0.34	0.01	++	−0.31	−0.01	++	−0.36	−0.19	++	0.11	0.1
4	−0.22	−0.01	+	0.18	0.004	NS	−0.21	−0.004	+	−0.35	−0.11	++	0.09	0.6
Left ventricular end diastolic pressure														
1	0.05	0.01	NS	−0.15	−0.02	NS	0.09	0.01	NS	0.16	0.38	NS	−0.04	−1.0
2	0.15	0.02	NS	0.28	0.02	+	−0.11	−0.008	NS	−0.08	−0.10	NS	−0.01	−0.
3	0.05	0.01	NS	0.14	0.01	NS	−0.07	−0.006	NS	−0.05	−0.08	NS	−0.004	−0.1
4	0.06	0.009	NS	−0.04	−0.003	NS	−0.13	−0.009	NS	0.09	−0.10	NS	0.11	0.5

Abbreviations r coefficient of correlation b slope of the equation + P < 0.01 > 0.001 ++ P < 0.001 x 1 5 LVSP LVEDP max dp dt lt ventricular systolic pressure LVEDP left ventricular end diastolic pressure Intervals and indices symbols as mentioned in the text

Table II Correlations between per cent changes in left ventricular systolic pressure max dp/dt and left ventricular end diastolic pressure and index 2 of 22 ventricular premature beats corresponding to one subject *

Post extra sys tolic beats	R EX r	R EX b	R EX P	EX R r	EX R b	EX R P	Index 1 r	Index 1 b	Index 1 P	Index 2 r	Index 2 b	Index 2 P	Index 3 r	Index 3 b	Index 3 P	Index 4 r	Index 4 b	Index 4 P
Left ventricular systolic pressure																		
1	0.26	−0.002	NS	0.24	−0.002	NS	0.27	−0.02	NS	−0.25	−0.04	NS	0.21	−0.01	NS	0.08	0.006	[illegible]
2	0.26	−0.002	NS	0.23	0.002	NS	0.27	−0.01	NS	0.26	−0.03	NS	0.05	−0.003	NS	0.15	1.34	[illegible]
3	0.05	0.0007	NS	0.07	−0.001	NS	0.08	0.008	NS	0.03	0.007	NS	0.10	0.009	NS	−0.09	−1.09	[illegible]
4	0.01	−0.0002	NS	0.03	0.001	NS	0.001	0.000	NS	0.05	−0.009	NS	0.01	−0.001	NS	0.006	−0.0	[illegible]
Max dp/dt																		
1	0.02	0.06	++	0.90	−0.06	++	0.90	−0.46	++	0.94	−1.01	++	0.89	−0.42	++	0.91	5	++
2	0.70	−0.02	++	0.72	0.02	++	0.71	−0.18	++	0.69	−0.38	++	0.67	−0.16	++	0.66	[illegible]	++
3	0.74	−0.03	++	0.72	0.03	++	0.75	−0.22	++	0.74	−0.48	++	0.71	−0.20	++	0.0	6	++
4	0.42	−0.01	++	0.41	0.01	++	0.41	−0.13	++	0.53	−0.37	++	0.39	−0.12	++	0.43	18	++
Left ventricular end diastolic pressure																		
1	0.50	0.04	++	0.50	−0.04	++	0.50	0.031	++	0.51	0.73	++	0.46	0.28	++	0.61	−0	++
2	0.16	0.008	NS	0.21	−0.01	NS	0.16	0.06	NS	0.21	0.18	NS	0.10	0.03	NS	0.29	−14	
3	0.28	0.01	NS	0.28	−0.01	NS	0.25	0.11	NS	0.32	0.30	NS	0.26		NS	0.35	−19	+
4	0.57	0.04	++	0.53	0.05	++	0.54	0.35	++	0.56	0.77	++	0.54	0.33	++	0.6	−49	++

Symbols as in Table I

sures and max dp/dt were measured in the beat preceding the premature beat and in the four consecutive beats after it. Percentage changes were calculated taking the preextrasystolic beat as reference. The following intervals or indices were also calculated (1) R R preceding R R interval (2) R EX interval between the preceding beat and the extrasystole or coupling interval (3) EX R interval between the extrasystole and the following beat or postextrasystolic pause (Fig 1) (4) Index 1 R EX/R R, (5) Index 2 R EX/R EX+EX R (6) Index 3, R EX/EX R,

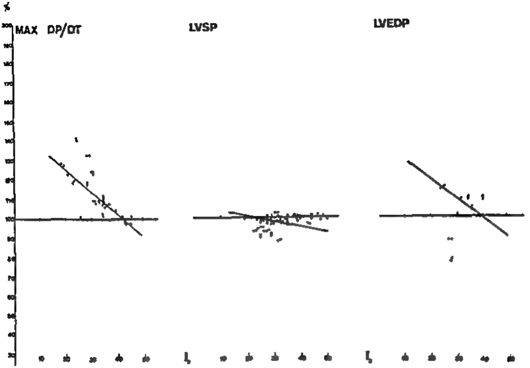

Fig 3 Regression lines of per cent changes in max dp/dt left ventricular systolic and end-diastolic pressures, and Index 2 in the first postextrasystolic beat of 102 premature beats.

rease of max dp/dt and left ventricular systolic ressure occurred in the second postextrasystolic eat as shown in Figs 1 and 4

On the other hand for early premature beats Index 2 > 0 35) the highest increase of max dp/dt occurred in the first postextrasystolic beat and later on proceeds with some degree of alternation

Left ventricular systolic pressure slightly decreases in the three postextrasystolic beats returning to the control value in the fourth one

Right and left ventricle stimulation The differences in cardiac response between premature beats elicited from either right or left ventricles are small as demonstrated in Table III and Fig 5

Discussion

The nature of postextrasystolic potentiation in the intact human heart has not been fully explained Results of animal experiences made in papillary muscle or in cardiopulmonary bypass are different from those found in the human heart

Studying the behavior of postextrasystolic ventricular and aortic pressures Beck and asso

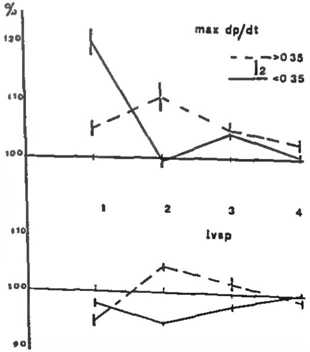

Fig 4 Per cent changes in max dp/dt (max dp/dt) and left ventricular systolic pressure (LVSP) of four postextrasystolic beats (numbers 1 to 4) when Index 2 is smaller (— early premature beats) or bigger (___ late premature beats) than 0.35 Vertical lines correspond to one standard error

Table III Correlations between per cent changes of max dp/dt and left ventricular systolic pressure and Index 2 when ventricular premature contractions were elicited from right or left ventricle'

Subject No	*Left ventricle*				*Right ventricle*			
	a	*b*	*r*	*No*	*a*	*b*	*r*	*No*
1 max dp/dt	2ɔ5	−3 3	−0 94	19	239	−3 5	−0 91	[illegible]
LVSP	106	−0 074	0 13	11	147	−12	−0 95	[illegible]
2 max dp/dt	163	−0 92	−0 37	4	195	−1 71	−0 68	9
LVSP	—	—	—	—	—	—	—	—
3 max dp/dt	162	−1 29	−0 53	7	159	−1 36	−0 90	[illegible]
LVSP	96	0 000	0 15	7	115	−0 02	0 99	[illegible]
4 max dp/dt	144	−1 3	−0 93	4	143	−1 01	−0 94	22
LVSP	77	0 72	0 45	4	100	−0 04	0 95	22

Abbreviations LVSP left ventricular systolic pressure a value Y when X = 0 x I y LVSP LVEDP max dp/dt Other symbols as in Tab

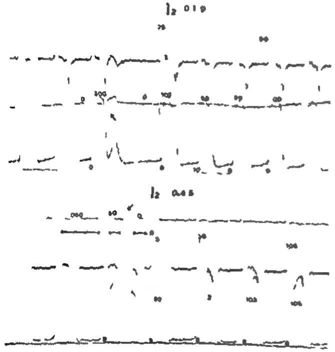

Fig 1 Early (Index 2 0 19) and late (Index 2 0 45) ventricular premature contractions Note that the highest value of max dp/dt in the late premature beat occurs in the second postextrasystolic one Each tracing shows ECG left ventricular pressure curve and its first derivative Numbers correspond to per cent changes except left ventricular end diastolic pressure which are expressed in absolute values Time intervals in milliseconds The arrows point to the ventricular premature beats

Early (Index 2 < 0 35) and late (Index 2 > 0 35) ventricular premature beats Another way to observe the left ventricular systolic pressure and max dp/dt behavior after a premature beat is to arbitrarily divide them into early and late premature beats It was found that in late extrasystoles (Index 2 < 0 35) the highest in

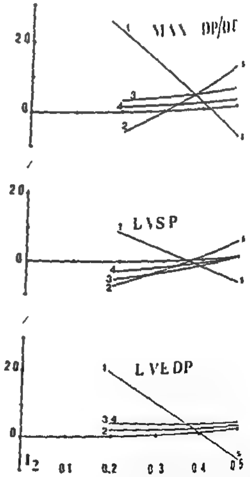

Fig 2 Upper Relationship between per cent changes in max dp/dt on the vertical axis and Index 2 (I) on the horizontal axis Slopes *1* to *4* indicate the first four postextrasystolic beats Note the change of slope between number *1* and *2* and *4* Data include 102 ventricular premature beats from patients Middle and lower Relationships between per cent changes of left ventricular systolic pressure (LVSP) and left ventricular end diastolic pressure (LVEDP) on the vertical axis and Index 2 (I) on the horizontal axis Correlation and regression coefficients may be seen in Table I S Statistical significance higher than 0 05

...nges in contractility the observation could be ...ained by different degrees of stimulation of ... carotid and aortic baroreceptors It has been ...onstrated in dogs that changes in nonpulsa... pressures in the isolated aortic arch or in the ...otid sinus region [14] produce clear changes in ...tractility Thus it is possible that long postex...systolic pauses of early ventricular premature ...ts would have lower aortic end diastolic pres...es which in turn would produce a higher ...ation of max dp/dt Unfortunately we did ... measure simultaneous aortic pressures and ...nnot substantiate this hypothesis This specu...ion would also explain the good correlations ...nd between changes in max dp/dt and the ...textrasystolic pause

...t is worth mentioning that the patient of ...ble II was a reserpinized hypertensive subject ...d he still maintained potentiation in the first ...stextrasystolic beat but did not show slope ...ersion phenomenon It has been demon...ated by Braunwald and associates [7] that reser...ne and beta adrenergic blockade failed to ...olish potentiation induced by paired stimula...on

Right and left ventricle stimulation From the ...esent data we cannot conclude that right or left ...ntricular stimulation would produce a higher ...otentiation This observation is in agreement ...ith some studies[...] which did not find signifi...ant differences in cardiac outputs when pacing ...as performed at different ventricular sites

The present observations indicate the need to ...easure potentiation by means of one of these ...dices since the results of a premature beat ...ould be very different according to its temporal ...elationship Heart sounds murmurs valve and ...ubvalvular gradients ventricular wall motion ...nd all phenomena affected by postextrasystolic ...otentiation should be related to those indices in ...rder to obtain reproducible results

Summary

The effect of different coupling indices and intervals that could theoretically affect postextrasystolic potentiation has been investigated A total of 150 ventricular premature beats corresponding to 20 patients submitted to routine cardiac catheterization were studied Only single ventricular premature contractions following at least four regular sinus beats were considered

Percentage changes in left ventricular systolic pressure end-diastolic pressure and max dp/dt were correlated against seven different indices and intervals Index 2 (coupling interval/coupling interval + postextrasystolic pause) gave the better correlations Besides this Index includes two intervals that were demonstrated to have statistical significance when individually considered It has been proved that in the first postextrasystolic beat the highest values of max dp/dt or left ventricular systolic pressure occurred in early ventricular premature beats giving a negative regression with Index 2 while in the second postextrasystolic beat the highest values of max dp/dt and left ventricular systolic pressure corresponded to late premature beats giving therefore positive regressions with Index 2 (slope inversion phenomenon) The third and fourth postextrasystolic beats had similar positive regressions but with progressively smaller slopes. Correlations between left ventricular end diastolic pressure and Index 2 were very poor

It is suggested that variations in baroreceptor activity could account for the different forms of potentiation observed in early and late extrasystoles

In five cases there were no consistent differences in potentiation when premature beats were elicited from either right or left ventricles

REFERENCES

1. Lagendorff O Untersuchungen am uberlabenden Saugethierhersen Pfluegers Arch. Ges. Physiol 61 291 1895
2. Cushny A. R and Matthews, S A. On the effects of electrical stimulation of the mammalian heart, J Physiol 21 213 1897
3. Woodworth R. S Maximal contraction staircase contraction refractory period and compensatory pause of the heart Am J Physiol 8 213 1902 1903.
4. Wiggers, C J Circulation in health and disease Philadelphia 1923 Lea & Febiger Publishers, p 521
5. Wiggers C J The pressure pulses in the cardiovascular systems London 1928 *Longmans, Green & Company* p 166
6. Cattell, M and Gold H Relation of rhythm to force of contraction of mammalian cardiac muscle Am J Physiol. 133 307 1941
7. Hoffman B F Bindlev E and Suckling E E Postextrasystolic potentiation of contraction in cardiac muscle Am J Physiol 185 95 1956
8. Hoffman B F and Kelly J J Effects of rate and rhythm on contraction of cat papillary muscle Am. J Physiol. 197 1199 1959
9. Siebens A A Hoffman B F Cranefield P F, and Brooks C Mc Regulation of contractile force during ventricular arrhythmias, Am J Physiol. 147 971 1959
10. Hoffman B F Bartelstone H J Scherlog B J et al Effects of postextrasystolic potentiation in normal and failing hearts Bull. N Y Acad. Med 41 498 1965
11. Lendrum B., Feinberg, H Boyd E and Kats L. N Rhythm effects on contractility of the beating isovolumic left ventricle Am J Physiol. 199 1115 1960

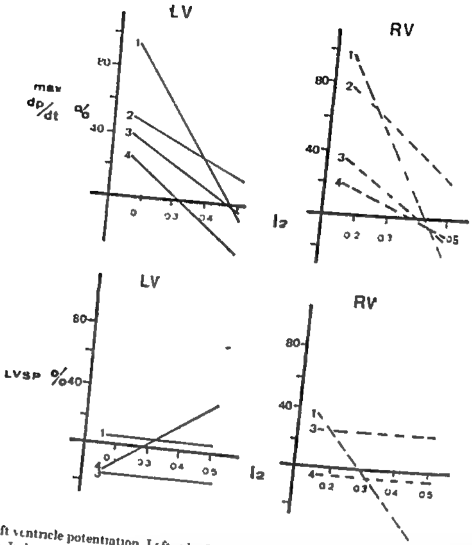

Fig 5 Right and left ventricle potentiation Left side Per cent changes in max dp/dt and left ventricular systolic pressure (LVSP) vs Index 2 (I) when ventricular premature beats are elicited from the left ventricle (LV,—) Right side The same relationships when the ventricular premature beats are elicited from the right ventricle (RV) Each studied patient has a number in the figure See regressions in Table III

ciates[1] could not explain completely the different patterns observed

Our statistical analysis for the different intervals and indices which could potentially affect postextrasystolic potentiation gave better correlations with Index 2 (coupling interval/coupling interval + postextrasystolic pause) (Tables I and II) This Index could be defined as the relationship between degree of prematurity and duration of postextrasystolic pause This later interval will vary in relation to heart rate and will influence aortic diastolic pressure These factors could affect cardiac contractility by different ways and mechanisms[8 14 16]

In the presence of very little changes in systolic pressure significant elevations of max dp/dt should correspond to an increase in contractility providing left ventricular end diastolic pressure does not change In our study the regression line of left ventricular end diastolic pressure and Index 2 was similar to the one of max dp/dt and Index 2 however there was a great dispersion of data (Table I Fig 3) In the patient of Table II the left ventricular end diastolic pressure and Index 2 regression line was positive and different from the one observed in the whole group (Figs 2 and 3) Moreover changes in left ventricular end diastolic pressure did not correlate with changes in left ventricular systolic pressure or max dp/dt All these reasons lead us to believe that the influence of left ventricular end diastolic pressure on max dp/dt was not significant

The slopes of the regression lines corresponding to changes in left ventricular systolic pressure and max dp/dt against Index 2 changed in sign after the first beat (slope inversion phenomenon) The second third and fourth postextrasystolic beats showed positive slopes different from the negative ones observed in the first postextrasystolic beat If these changes in max dp/dt reflect

...idence and morphology of carotid shudders ... valve disease

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...presence of systolic vibrations in the carotid ...se has been termed carotid shudder and it ... been noted in the majority of patients with ...anced aortic stenosis Although earlier ...hors [2] have stated that carotid shudders do ...ssionally occur in patients with aortic insuffi...ncy current cardiology texts do not cite this ...ationship[3] Moreover little is known about ... incidence and morphology of carotid shudders ... patients with aortic valve disease

In order to document the incidence and to ...aracterize the morphology of carotid shudders ... patients with aortic valve disease we studied ...e carotid pulse tracings of 73 patients with ...vanced aortic valve disease documented by ...rdiac catheterization

...aterials and methods

Patients Seventy three patients were chosen ... the study All patients had undergone right ...d left heart catheterization and cineangio...aphic study to evaluate their aortic valve ...sease Three groups of patients were defined In ...roup 1 30 patients (19 males and 11 females ...ean age 45 range 10 to 80 years) were found to ...ave aortic stenosis of moderate to severe degree ...aortic valve area less than 1 2 sq cm) No ...atient with mild aortic stenosis alone was ...ncluded These 30 patients had no or minimal aortic regurgitation by aortic root cineangiography In Group 2 29 patients (18 females and 11 males mean age 43 range 15 to 64 years) had aortic insufficiency graded as 3+ to 4+ by aortic root cineangiography Small aortic valve gradients were present in three patients (30 20 10 mm Hg peak to peak) all of whom had 4+ aortic regurgitation on aortic root cineangiography In Group 3 14 patients (9 males and 5 females mean age 42 range 11 to 71 years) had mixed aortic stenosis and insufficiency All 14 patients had 2+ aortic insufficiency by aortic root cineangiography Aortic valve gradients ranged from 15 to 100 mm Hg peak to peak (mean = 54 mm Hg)

Methods Carotid pulse tracings were recorded on the day preceding cardiac catheterization while the patients were resting quietly in the supine position Carotid pulse tracings were recorded along with 100 Hz second left intercostal space phonocardiograms and Lead II of the electrocardiogram A commercially available Siemens Elema transducer (Model E117E) with a frequency response of 0 to 30 Hz and a Siemens Mingograf 34 recorder with paper speeds of 50 and 100 mm per second were employed Cardiac catheterization was performed in the standard manner[4]

Carotid pulse tracings and phonocardiograms were examined and categorized without prior knowledge of the patient s diagnosis or catheterization result Non paired Student s t tests were performed with the aid of a Wang calculator A value of $p < 0.025$ or less was accepted as significant

Results

Carotid shudders were of two types coarse and fine (Fig 1) As noted in Table I and Fig 2 two thirds of the patients with aortic stenosis had

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12 Beck W Chealer E and Schrire V Postextrasystolic ventricular pressure responses Circulation 44 523 1971
13 Cranefield P F The force of contraction of extrasystoles and the potentiation of force of the postextrasystolic contraction A historical review Bull N Y Acad Med 41 419 1965
14 Bowyev A F Allen R L Schmidt P L and Johns V J Contractile element velocity during pacemaker tachycardia in man Circulation 44(Suppl II) 144 1971
15 Hainsworth R and Karim F Inotropic responses of the left ventricle to changes in aortic arch pressures in anaesthetized dogs J Physiol 223 213 1972
16 Glick G Lewis R M and Segal M G Importance of the carotid sinus baroreceptors in the regulation of myocardial performance J Clin Invest 50 1116 1971
17 Braunwald E Ross J Jr Sonnenblick E H et al Slowing of heart rate electroaugmentation of ve[illegible] performance and increase of myocardial [illegible] consumption produced by paired electrical stim[illegible] Bull N Y Acad Med 41 481 1965
18 Benchimol A and Liggett M S Cardiac [illegible]namics during stimulation of right atrium right ve[illegible]cle, and left ventricle in normal and abn[illegible] Circulation 33 933 1966
19 Barold S S Ninhart J W Hildner F J and [illegible] P Hemodynamic comparison of endocardial pa[illegible] outflow and inflow tracts of right ventricle [illegible] Cardiol 23 697 1969
20 Mendel D A practice of cardiac catheterization [illegible] and Edinburgh 1968 Blackwell Scientific Publ[illegible] p 218
21 Fry D L Physiologic recording by modern instr[illegible] with particular reference to pressure recording P[illegible] Rev 40 4 1960

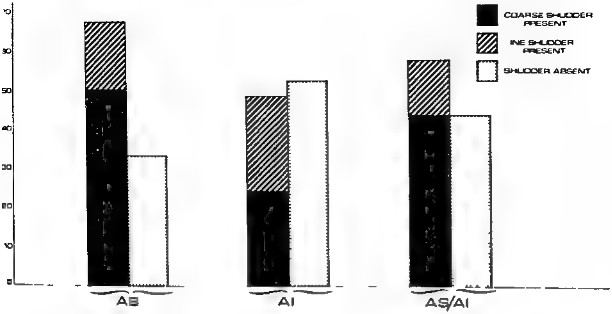

Fig 2 Incidence of fine and coarse shudders in patients with aortic stenosis (*AS*) aortic insufficiency (*AI*) and mixed aortic stenosis and insufficiency (*AS/AI*)

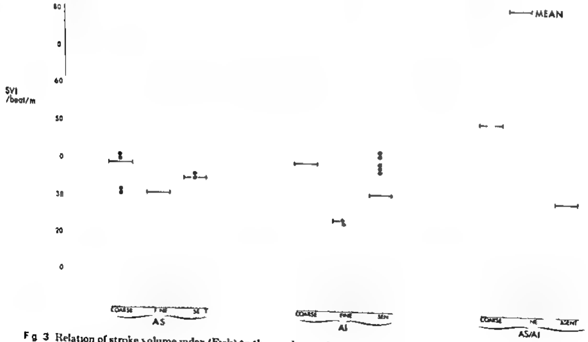

Fig 3 Relation of stroke volume index (Fick) to the incidence of carotid shudders in patients with aortic stenosis (*AS*) aortic insufficiency (*AI*) and mixed aortic stenosis and insufficiency (*AS/AI*)

respect from patients with fine or coarse shudders. Patients with mixed aortic stenosis and insufficiency demonstrated significantly higher ($p < 0.02$) stroke volume index if they had a coarse shudder than if they had none (Fig 3 Table II)

Systolic ejection murmur amplitude and the ratio of systolic ejection murmur amplitude to S_2 amplitude were not predictive of the presence of carotid shudders in patients with aortic stenosis or in patients with mixed aortic stenosis and insufficiency (Figs 4 and 5 Table II) In patients

Fig 1 Two examples of fine (left) and coarse (right) shudders recorded from four patients with advanced aortic valve disease

Table I Incidence of carotid shudders in patients with documented aortic valve disease

Patient group	Coarse shudder present		Fine shudder present		Shudder absent	
	No	%	No	%	No	%
Aortic stenosis (n = 30)	15	50	5	17	10	33
Aortic insufficiency (n = 29)	7	24	7	24	[illegible]	[illegible]
Aortic stenosis/aortic insufficiency (n = 14)	[illegible]	43	2	14	6	43

Table II Statistical comparison of hemodynamic and phonocardiographic parameters in patients with aortic valve disease with and without carotid shudders*

Groups compared	AS		AI	AS/AI
Coarse shudder vs fine shudder	SVI	NS	$p < 0.01$	—
	SEMA	NS	$p < 0.001$	NS
	SEMR	NS	NS	NS
Coarse shudder vs no shudder	SVI	NS	NS	$p < 0.02$
	SEMA	NS	$p < 0.01$	NS
	SEMR	NS	$p < 0.02$	NS
Fine shudder vs no shudder	SVI	NS	NS	—
	SEMA	NS	NS	NS
	SEMR	NS	NS	NS

AS = aortic stenosis AI = aortic insufficiency AS/AI = aortic stenosis/insufficiency SVI = forward stroke volume index (Fick) SEMA = systolic ejection murmur amplitude SEMR = systolic ejection murmur amplitude/S amplitude

carotid shudders Three quarters of the shudde were coarse and one quarter were fine

Carotid shudders were recorded in approxi mately half of the patients with aortic insuffi ciency Half of the shudders were coarse (Table I Fig 2) Two of the three patients with sr aortic valve gradients had no recordable caro shudder the third had a coarse shudder I patients with mixed aortic stenosis and insuf ciency carotid shudders were recorded in 57 p cent (Table I Fig 2) Three quarters of the shudders were coarse

A chi square analysis revealed no significa differences between the three patient groups wi respect to the incidence of coarse or fine shud ders

One hemodynamic and two phonocardiograph ic parameters were found to correlate with th existence of carotid shudders in the three group of patients forward stroke volume (Fick) phono cardiographic systolic ejection murmur ampl tude and the ratio systolic ejection murm amplitude/S_2 amplitude

Forward stroke volume (Fick) did not differ i patients with aortic stenosis irrespective of th presence or absence of coarse or fine shudde (Fig 3 Table II) In patients with aortic insuffi ciency however forward stroke volume wa significantly greater ($p < 0.01$) in patients with coarse shudders than in those with fine shudders Patients without shudders did not differ in th

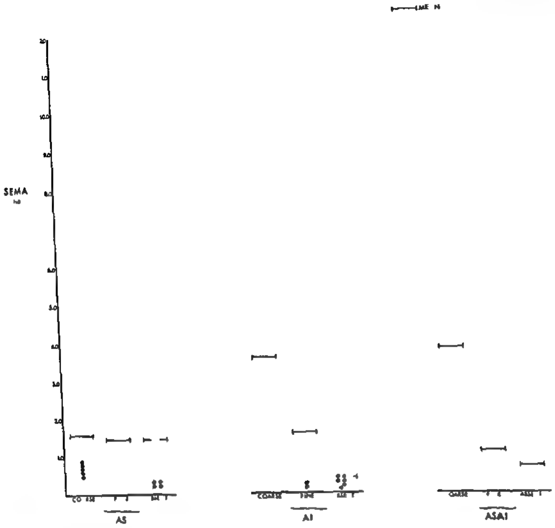

Fig 5 Relation of phonocardiographic ratio (systolic ejection murmur amplitude/S amplitude) to the incidence of carotid shudders in patients with aortic stenosis (*AS*) aortic insufficiency (*AI*) and mixed aortic stenosis and insufficiency (*AS/AI*)

…ned them Some noted the presence of carotid shudders others failed to comment on this finding It is therefore difficult to draw any conclusions concerning the clinical palpability of the carotid shudders which were recorded in these patients. In our personal experience coarse shudders are invariably palpable whereas fine shudders are at times felt and at other times not perceived

Mechanism of carotid shudders A detailed analysis of the mechanism of carotid shudders is not warranted on the basis of our preliminary data in a relatively small group of patients Several interesting observations do require comment however Patients with aortic stenosis (with or without insufficiency) can have recordable shudders despite modest recordable systolic ejection murmurs Indeed systolic ejection murmur amplitudes and ratios did not correlate with the presence of carotid shudders in these patients In patients with aortic insufficiency however systolic ejection murmur measurements were modestly predictive of the presence of a carotid shudder A tendency toward larger forward stroke volume indices in patients with aortic insufficiency and coarse carotid shudders suggests that the louder systolic ejection murmurs in these patients could have been partly secondary to a larger left ventricular stroke output Unfortunately total (angiographic) stroke volume was available in only a few of these patients

Flexural wall vibrations are radial vibrations

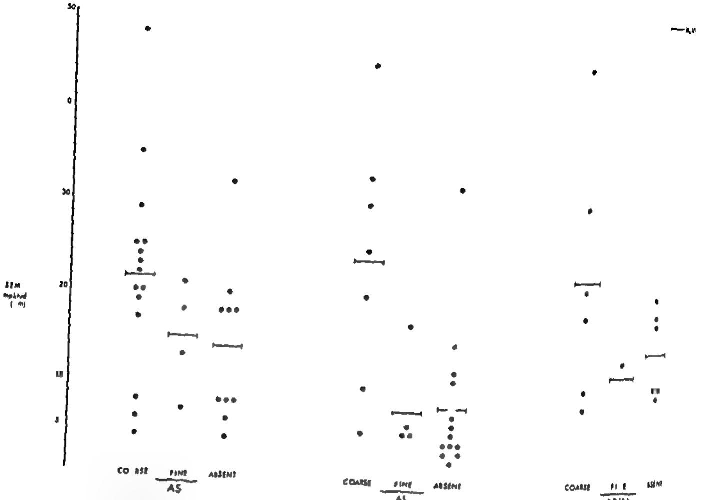

Fig 4 Relation of phonocardiographic systolic ejection murmur amplitude to the incidence of carotid shudders in patients with aortic stenosis (AS) aortic insufficiency (AI) and mixed aortic stenosis and insufficiency (AS/AI)

with aortic insufficiency, these two phonocardiographic measurements were significantly greater (Figs 4 and 5, Table II) in patients with coarse shudders compared to those without shudders ($p < 0.01$ $p < 0.02$) and in patients with coarse shudders compared to those with fine shudders ($p < 0.001$)

Discussion

Current standard references provide little or no information about the incidence and morphology of recorded carotid shudders in aortic valve disease [3,7] What little commentary does exist in these and earlier sources simply states that carotid shudders can and do occur commonly in patients with aortic stenosis [1,7] No mention is made of carotid shudders occurring in patients with aortic insufficiency in current reference texts [3,7] Smith and associates[2] described a single patient with a carotid shudder who was felt clinically to have predominant aortic insufficiency

In the present work we report the incidence of recorded carotid shudders in patients with three forms of documented aortic valve disease aortic stenosis aortic insufficiency, and mixed aortic stenosis and insufficiency As noted in Table I and Fig 2 two types of carotid shudder occurred in our three groups of patients coarse shudders and fine shudders The over all incidence of carotid shudders was essentially the same in each of the patient groups Patients with predominant aortic stenosis and mixed aortic stenosis and insufficiency had coarse shudders more frequently than patients with predominant aortic insufficiency This difference however, was not statistically significant in a population of 73 patients Perhaps with a larger group of patients there might be a significantly higher percentage of individuals with coarse shudders in the group with predominant aortic stenosis

This study employed recorded carotid pulse tracings Since our 73 patients were seen over a 10 year period many different cardiologists exam

uction of hospital mortality rate of acute myocardial rction with glucose-insulin-potassium infusion

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utions of glucose insulin potassium (GIK) e for many years been advocated as a poten l metabolic support for ischemic jeopardized ocardium in the early hours following an acute ocardial infarction The efficacy of these utions and the possible mechanisms of action e however remained controversial Re rted studies have differed in patient selection route of GIK administration in concentration various components administered and in tionale for the use of the GIK solution One tential benefit of GIK in the early postinfarct riod might be the suppression of plasma free tty acids (FFA) known to be present in gher than usual concentrations during this peri and reported to enhance ventricular ritability to increase myocardial oxygen onsumption and to depress myocardial echanical performance

This report describes the development of a technique for GIK administration in a pilot group of 70 patients with unequivocal acute myocardial infarction (AMI) The objective of GIK adminis tration was to suppress plasma FFA below the established myocardial FFA uptake threshold and to simultaneously increase the availability of carbohydrate as a myocardial substrate The outcome of this initial cohort of 70 GIK treated patients will be compared with that of a group of 64 patients managed in the same coronary care unit during the year prior to commencement of the GIK infusions

Patient population

Clinical assessment All patients included in this study were admitted with suspicion of acute myocardial infarction to the Myocardial Infarc tion Research Unit (MIRU) of the University of Alabama Medical Center Patients in both the control and GIK treated groups were evaluated and managed by at least one of the two senior authors (R O R C E R) Each patient had unequivocal evidence of acute myocardial infarc tion defined as typical history together with (1) electrocardiographic (ECG) evidence of trans mural infarction (evolutionary ST T changes with Q wave development) as well as elevated serum glutamic oxalacetic transaminase (SGOT) (normal 0 to 40 I U per liter) or (2) ECG evidence of subendocardial injury (ST T changes only) with marked elevation of SGOT (150 I U

rom the D ision f Cardiol gy Departm nt of Medicin Uni rsity f Alabama Medical Ce ter Uni rsity Stat on, and th Vete ns dministr tion Hospital, Birmingham Ala.

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which are well transmitted along liquid filled tubes[9] This acoustic observation means that once the vibrations of a murmur are 'impressed' onto the wall of the aorta, they tend to travel along this vessel with only modest attenuation[9,10] It is these flexural wall vibrations which are recorded (and felt) as a carotid shudder and heard as a systolic ejection murmur The data presented above suggest that flexural wall vibrations of sufficient intensity to produce a carotid shudder occur during left ventricular systolic ejection in the majority of patients with moderate or severe aortic stenosis In patients with aortic insufficiency, it would seem that a loud flow related systolic ejection murmur can also create radial vibrations in the aortic wall of sufficient intensity to produce a carotid shudder

The present observations emphasize the fact that given a patient with aortic valve disease and a carotid shudder one cannot predict on the basis of this finding whether that individual has predominant stenosis insufficiency or mixed stenosis and insufficiency

Summary

The incidence and morphology of shudders in carotid arterial pulse tracings were examined in 73 patients with aortic valve disease documented by cardiac catheterization Two forms of carotid shudder were recorded coarse and fine Shudders were present in 67 per cent of patients with aortic stenosis 48 per cent of patients with aortic insufficiency and 57 per cent of patients with mixed aortic stenosis and insufficiency No signif icant difference existed among these three groups of patients with respect to the over all incidence of carotid shudders or with respect to the inci dence of coarse or fine shudders In patients with aortic insufficiency stroke volume index (Fick) and phonocardiographic systolic ejection mur amplitude were significantly greater (p< p < 0 001, respectively) in those with co carotid shudders compared with those m festing fine or absent shudders Loud f related, systolic ejection murmurs of a insufficiency are capable of producing r vibrations in the aortic wall which are recorded carotid shudders The finding of a carotid sh in a patient with aortic valve disease does n enable the physician to distinguish betw stenosis, insufficiency, or mixed stenosis a insufficiency

REFERENCES

1 Duchosal P W Ferrero C Leupin A and Urdan E Advance in the clinical evaluation of aortic by arterial pulse recordings of the neck Am Heart 51 861 1956
2 Smith J E Hsu I Evans J M and Lederer L Aortic stenosis A study with particular reference to indirect carotid pulse recording in diagnosis Am Heart J 58 527 1959
3 Hurst J W and Schlant R C Examination of the arterial pulse *in* Hurst J W Logue R B Schlant R C and Wenger N K editors The Heart New 1974 McGraw Hill Book Company Inc
4 Friedberg C K Diseases of the Heart Philadelphia 1967 W B Saunders Company
5 Braunwald E Chronic valvular heart disease Beeson P B and McDermott W editors Textbook Medicine Philadelphia 1971 W B Saunders Company
6 Tavel M E Clinical Phonocardiography and External Pulse Recording Chicago 19?? Year Book Medical Publishers Inc
7 Massumi R A Zelis R Ali N and Mason D T External venous and arterial pulses *in* Weissler A M editor Noninvasive Cardiology New York 19?4 Grune & Stratton Inc
8 Grossman W editor Cardiac Catheterization and Angiography Philadelphia 1974 Lea & Febiger Publishers
9 Callaway D B Tyzzer F G and Hardy H C Resonant vibrations in a water filled piping J Acoust Soc Am 23 224 1951
10 Bruns D L A general theory of the causes of murmurs in the cardiovascular system Am J Med 27 1959

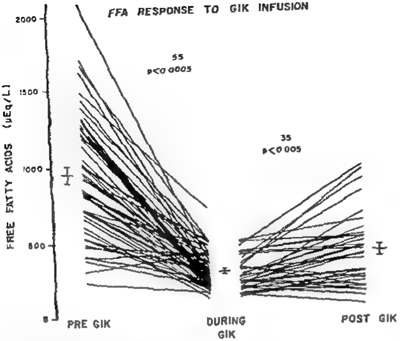


Fig 1 During GIK infusion the mean plasma FFA fell from pre GIK level of 944 ± 57 to 260 ± 16 μEq per liter (p < 0 0005) During the 24 hours following discontinuation of GIK FFA were observed to rebound to a mean level of 4 0 ± 39 μEq per liter (p < 005)

t the two patient populations were evenly tched for the subsequent mortality analysis

thod

GIK treated patient group Following informed nsent and as soon as possible after admission to e *MIRU* patients underwent right heart cathe rization via an antecubital cutdown with inser on of a triple lumen Swan Ganz thermodilution theter into the pulmonary artery Baseline easurements of vital signs pulmonary artery ressure plasma FFA glucose blood urea nitrogen (BUN) creatinine electrolytes osmo arity and SGOT were obtained Through the ght atrial port of the Swan Ganz catheter the atient was given a bolus of 20 ml of D50W and 5 1 of regular insulin followed immediately by an nfusion containing 300 Gm of glucose 50 U of egular insulin and 80 mEq of KCl per liter of 10 delivered at a constant infusion rate of 0 5 to 2.0 ml. per kilogram per hour (mean 1 26 ± 0 04 ml. per kilogram per hour) To maintain patency of the Swan Ganz catheter a solution containing 5 000 U of heparin per liter of 0 5N saline was infused continuously at 10 c c per hour into the pulmonary artery port 10 c c aliquots of this solution were flushed vigorously into the right atrial and pulmonary artery ports of the catheter at hourly intervals

Baseline measurements were repeated at 4 to 6 hour intervals during the 48 hour GIK infusion in all patients and for 48 hours following GIK discontinuation in 21 patients All patients had continuous rhythm monitoring and arrhythmias received routine pharmacological therapy[20] Patients were kept at bed rest in the supine position and were allowed only clear liquids as oral intake during the 48 hour GIK infusion

Control patient group Patients were managed in conventional fashion as previously described by Dowling and associates Invasive hemody namic monitoring was employed in 19/64 (30 per cent) of the total control patient group including 10/19 (53 per cent) of the control patient nonsur vivors

Assay methods Glucose BUN creatinine electrolytes and SGOT were determined by stan dard automated techniques on Technicon Model 1260 and Model AAII autoAnalyzers Serum osmolarity was determined by the freezing point depression method on an automatic osmometer (Osmette A Precision Systems Inc) Free fatty acids were analyzed by the method of Dun combe[21]

Table I Comparison of patient groups

Parameter	*GIK*	*Control*
No of patients	70	64
Sex	59M 11F	47M 17F
Age		
Mean	53 ± 1*	61 ± 1
Range (yr)	24–78	36–83
History of angina	4[illegible] (71%)	34 (53%)
History of prior infarct	23 (33%)	18 (28%)
Time lapse from onset of pain to commencement of study (hr)	7.8 ± 0.4	7.4 ± 1.0
range	[illegible]	[illegible]
Admission systolic BP	127 ± 4	130 ± 4
S_3 gallop on admission	33 (47%)	26 (41%)
Cardiogenic shock on admission	11 (16%)	10 (16%)
Radiological evidence of		
Abnormal heart size	24 (34%)	31 (48%)
Abnormal lung fields	24 (34%)	22 (31%)
ECG showing		
Infarct location		
Anterior	38 (54%)	27 (42%)
Inferior	32 (46%)	33 (52%)
Undetermined	0	4 (6%)
Infarct extent		
Subendocardial	4 (6%)	4 (6%)
Transmural	66 (94%)	60 (94%)
Prognostic indices (means)		
Killip score	2.2 ± 0.1	2.1 ± 0.1
Peel score	14.[illegible] ± 0.7	14.0 ± 0.7
Norris score	6.6 ± 0.4	6.8 ± 0.3

* p < 0.001 (GIK vs control) No other parameters differed significantly between patient groups Continuous parameters are reported as mean ± S E M

Table II Summary of clinical parameters [illegible]cluded in prognostic indices*

Parameter	*Killip*	*Peel*	*N[illegible]*
Age	0	X	X
History of			
Myocardial infarction	0	X	X
Angina	0	X	X
Dyspnea on exertion	0	X	0
Hypertension	0	X	0
Other cardiovascular disease	0	X	0
Physical examination			
Heart rate	0	X	0
Systolic blood pressure	X	0	X
Shock	X	X	0
S_3 gallop	X	X	0
Râles	X	X	0
Dyspnea edema orthopnea hepatomegaly	0	X	0
Laboratory data			
ECG			
Infarct location	0	0	X
Infarct extent	0	X	X
Dysrhythmia	0	X	0
Chest x ray			
Heart size	[illegible]	0	X
Lung fields	X	0	X

Abbreviations X = parameter included in prognostic index, [illegible] parameter not included in prognostic index. More detailed descrip[illegible] of the relative weightings of the various parameters are described [illegible] original reports by Killip Peel and Norris and their associa[illegible]

per liter or greater) and typical time wise evolution of the altered enzyme

The control patients were a retrospectively analyzed group of 64 consecutive patients satisfying the above criteria and admitted to the MIRU during the calendar year prior to the onset of the GIK study The GIK treated patients were a prospectively analyzed nonconsecutive series of 70 patients, admitted to the MIRU from November 1972 through December 1974, who received a GIK infusion beginning within 15 hours (mean 7 8 ± 0 4 hours) of the onset of their chest pain (or initial symptom of myocardial infarction)

Comparison of the two patient groups is presented in Table I The GIK group had a mean age of 53 ± 1 years compared to 61 ± 1 years for the control group (p < 0 001) otherwise the two groups had remarkably similar clinical characteristics Time of onset of chest pain was not uniformly well documented in the control group, however in the 47 control patients with docu[illegible] mentation the mean interval from pain onset [illegible] admission to the MIRU was not significantl[illegible] different from the interval from first pain [illegible] commencement of GIK infusion in the GI[illegible] group The GIK recipients included 16 patien[illegible] with history of glucose intolerance of these, thre[illegible] were insulin dependent four were dependent o[illegible] oral hypoglycemic agents, and the remainder were receiving no hypoglycemic therapy o[illegible] admission

Assessment by prognostic indices In order to assess the relative severity of each patient's infarction and his prognosis data obtained from each patient s admission clinical evaluation were scored according to the prognostic indices of Killip and Kimball,[27] Peel and associates [illegible] and Norris and associates [29] A comparison of the clinical parameters scored by these indices is presented in Table II The mean prognostic scores calculated independently by the Killip Peel and Norris methods were remarkably similar between the GIK and control group (Table I) confirming

III Distribution of patients into prognostic index subgroups

Killip subgroup No	GIK group				Control group				Killip		
	No	Deaths		Mort rate (%)	No	Deaths		Mort rate (%)	No	Deaths obs	Mort. rate (%)
		Obs	Exp			Obs	Exp				
Killip index											
	19	0	1 1	0	16	2	1 0	12	81	5	6
	32	3	5 4	9	33	7	5 6	21	96	16	17
	7	1	2 7	14	5	[illegible]	1.9	40	26	10	38
	12	7	9 7	58	10	8	8 1	80	47	38	81
Totals	70	11‡	18 9	16	64	19†	16 6	30	250	69	28

Peel subgroup (score)	GIK group				Control group				Peel		
	No	Deaths		Mort rate (%)	No	Deaths		Mort rate (%)	No	Deaths obs	Mort rate (%)
		Obs	Exp			Ob	Exp				
Peel index											
(0-8)	8	0	0 2	0	12	0	0 3	0	203	5	2
(9 12)	22	0	2 8	0	12	2	1.5	17	176	22	12
(13 16)	16	1	3 8	6	22	5	5 2	23	139	33	24
(≥17)	4	10	15 3	42	18	12	11.5	67	110	70	64
Totals	70	11†	22 1	16	64	19†	18 5	30	628	130	21

Norris Subgroup No (score)	GIK group				Control group				Norris		
	No	Deaths		Mort rate (%)	No	Deaths		Mort rate (%)	No	Deaths obs	Mort rate (%)
		Obs	Exp			Obs	Exp				
Norris Index											
1 (< 4)	16	0	0 5	0	6	0	0 2	0	132	3	2
2 (4 5)	20	0	1 6	0	25	6	2 0	4	200	16	8
3 (6-7)	13	1	2 9	8	18	4	3 5	5	1 9	35	22
4 (8-9)	10	3	4 0	30	10	4	4 0	40	128	51	40
5 (10-11)	6	4	3 9	67	3	1	2 0	33	66	43	65
6 (≥ 12)	5	3	3 9	60	4	4	3 1	100	72	56	78
Totals	0	11	16 8	16	64	19†	14 8	30	57	205	28

Abbreviations Obs. = observed number of patient deaths Exp = expected number of patient deaths computed as the product of number and per cent deaths from Killip Peel, Norris.
$p < 0.005$ (obs vs exp number of patient deaths)
$p < 0.03$ (obs vs exp number of patient deaths)
$p < 0.10$ (obs vs exp number of patient deaths)
† Not significant ($p > 0.10$) (obs vs exp number of patient deaths)

of Killip, Peel and Norris respectively was not significantly different from the observed mortality rate ($p > 0.10$) However the observed mortality rate in the GIK treated group was 42 per cent ($p < 0.03$) 50 per cent ($p < 0.005$) and 35 per cent ($p < 0.10$) less than predicted by the Killip Peel and Norris indices respectively (chi square one sided test)

Mortality rates in the individual Killip Peel and Norris subgroups are shown graphically in Figs 3 4 and 5 The figures show that the most striking mortality reduction occurred with GIK treatment of the least complicated patients (Killip groups I and II Peel score 1 to 16 Norris score 1 to 7) The over all mortality rate of the control group was 29 7 per cent (19/64) and that of the GIK group 15 7 per cent (11/70) the latter representing a statistically significant mortality reduction in the GIK recipients ($p < 0.05$)

Clinical and pathological characteristics of

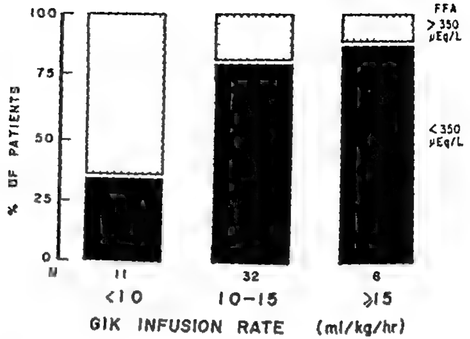


Fig 2 Effect of GIK infusion rate on FFA GIK in the previously described concentration reduced mean plasma FFA to subthreshold levels (< 350 μEq per liter) most consistently when infused at rates of 1 5 ml per kilogram per hour or greater The only patient not suppressed to subthreshold level with this dosage was receiving heparin in therapeutic doses

Data analysis The hospital mortality rates of the GIK and control groups were computed and further analyzed by the subgroupings of Killip Peel, and Norris to ascertain which clinical type of infarction might be most benefited by GIK infusion

Statistical analysis Data are reported as means ± S E M Student s t test was used to assess differences between means of independent observations, the chi square test was used to assess differences between proportions

Results

Optimal GIK infusion rate Fig 1 illustrates the dramatic FFA fall during GIK infusion FFA fell in every patient having elevated levels before GIK infusion was initiated Mean pretreatment FFA was 944 ± 57 μEq per liter and average FFA during GIK treatment was 289 ± 16 μEq per liter ($p < 0.0005$) (normal FFA levels are reported as 521 ± 128 (S D) μEq per liter[18]) Also shown in Fig 1 is the FFA rebound noted during the 24 hours following discontinuation of GIK infusion

FFA levels during GIK infusion correlated in a general fashion with GIK infusion rate ($r = 0.56$ $p < 0.0001$, $n = 51$) Fig 2 graphically demonstrates that the plasma FFA was most consistently reduced to subthreshold levels (< 350 μEq per liter[26]) when the GIK infusion rate was ≥ 1 5 ml per kilogram per hour Indeed only one of the patients infused at that rate had a mean FFA during the infusion of higher than 304 μEq per liter and that patient following a pulmonary embolus, was receiving therapeutic doses heparin an agent known to elevate FFA levels by activation of lipoprotein lipase [33,34]

Since Fig 1 demonstrated significant FFA reduction in every patient in whom FFA was initially elevated all patients have been included in the subsequent mortality analysis regardless of GIK flow rate since it is evident that the goal of FFA reduction was uniformly achieved albeit not to subthreshold levels in every case

Predicted vs observed mortality rates Table III presents the distribution of the GIK and control patients according to the prognostic index subgroupings of Killip Peel and Norris respectively Also included for comparison are the mortality data of Killip, Peel and Norris Distribution of patients into subgroups was similar among GIK controls and the Killip and Norris classifications ($p > 0.10$) In the Peel analysis patients were subdivided similarly between GIK and controls however both GIK and controls had a smaller proportion of patients in the first Peel subgrouping (uncomplicated infarcts) compared to Peel s patient population

In the control population the expected mortality rate derived from the original mortality data

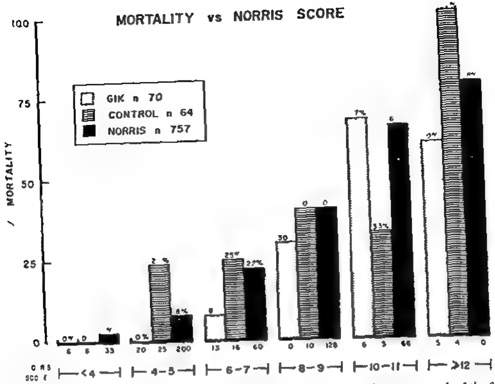


Fig 6 Mortality rate vs Norris score The GIK recipients had a reduced mortality rate in each of the 6 Norris subgroups compared to Norris original series and in five of the six subgroup compared to controls The magnitude of the Norris score is directly proportional to Norris estimate of the severity of the infarction based on admission clinical evaluation

and Fig 6 the GIK nonsurvivors had severe -iuse (two and three vessel) coronary artery sease Interestingly one of the GIK recipients u found at autopsy to have a congenitally sent left coronary artery with malnourished ft ventricular myocardium partially supplied / branches from the right coronary artery stem all of which were diseased (three vessel sease equivalent) None of the GIK nonsurvi ors was found to have uncomplicated single essel disease Coronary artery pathology in the ontrol group nonsurvivors on the other hand as more evenly distributed among one two nd 3 vessel stenoses (Fig 6)

Of the GIK recipients one patient (No 8) died f ruptured left ventricular free wall during his econd day of GIK infusion Another patient (No 1) experienced rupture of the interventricular eptum rapid hemodynamic decompensation and death 4 days following discontinuation of her 43 hour course of GIK Patient No 1 died following emesis and massive aspiration of gastric contents. Patient No 6 had anoxic encephalopathy flail chest, acute renal failure hyperkalemia and died in cardiogenic shock 12 hours following GIK discontinuation Of the control patients there were three deaths secondary to ruptured left ventricle (patients Nos 2 3 and 16)

Mortality rate related to history of prior myocardial infarction Fig 7 shows that there was a reduction of the mortality rate in GIK treated patients regardless of whether the patients had experienced a prior myocardial infarction However the reduction in mortality rate was most striking in patients not having had a prior myocardial infarction (fourfold reduction $p < 0.05$)

Complications

General. Complications of the GIK infusion were infrequent and chiefly included hyperglycemia and hyperkalemia Initial attempts at infusion of the GIK solution via the pulmonary artery port of the Swan Ganz catheter resulted in a pneumonitis-like radiographic pattern [35] This pattern cleared upon discontinuance of GIK subsequent patients infused via the right atrial port of the Swan Ganz catheter did not experience this complication Phlebitis at the infusion

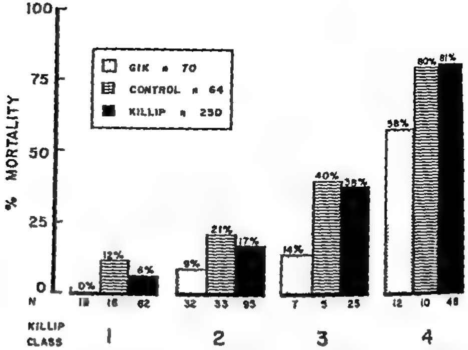


Fig 3 Mortality rate vs Killip class The GIK recipients had a reduced mortality rate in each of the 4 Killip classes compared to controls and to Killip's original series Class 1 = no congestive failure Class 2 = mild congestive failure (S3 gallop basilar rales) Class 3 = pulmonary edema Class 4 = cardiogenic shock

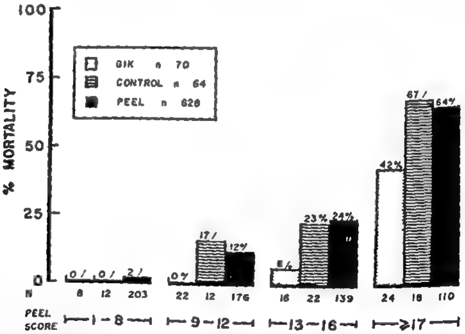
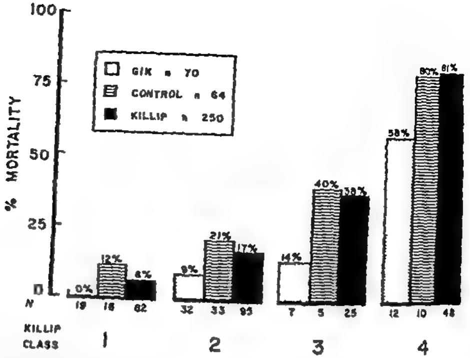


Fig 4 Mortality rate vs Peel score The GIK recipients had a reduced mortality rate in each of the 4 Peel subgroups compared to controls and to Peel's original series The magnitude of the Peel score is directly proportional to Peel's estimate of the severity of the infarction based on admission clinical evaluation

nonsurvivors Table IV describes the clinical presentation, prognostic scores, and coronary anatomy of the nonsurvivors in the GIK and control groups The mean ages of the GIK and control group nonsurvivors were similar Mean prognostic index scores of GIK nonsurvivors were uniformly higher than those of the control group nonsurvivors but these differences were statisti- cally significant only in the Norris scor (p = 0 056)

Postmortem and/or angiographic documenta tion of coronary artery anatomy was available in nine of the 11 GIK nonsurvivors and in 15 of the 19 control group nonsurvivors As shown in Tabl



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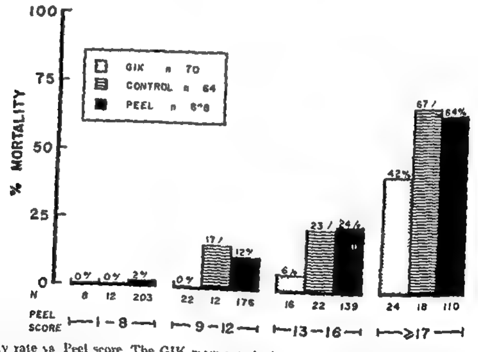

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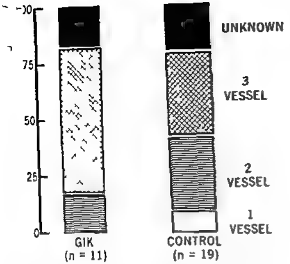

Extent of coronary artery disease in nonsurvivors from coronary angiography or from postmortem studies ed that the GIK nonsurvivors had a greater preponder of severe diffuse (two and three-vessel) coronary artery ase compared to controls

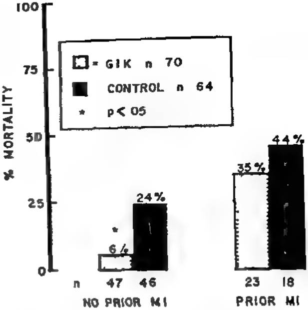

Fig 7 Mortality rate and prior myocardial infarction Although the over all mortality rate was reduced with GIK infusion patients with no prior history of myocardial infarc tion had the most striking reduction in mortality rate

Osmolarity Serum osmolarity was measured ring GIK infusion in 62 of the 70 GIK recip ts and averaged 284 ± 2 mOsm per liter ormal range 280 to 305 mOsm per liter) In ly two patients was the serum osmolarity thologically elevated (315 and 354 mOsm per er—these were the two insulin dependent abetic patients previously mentioned whose IK infusion was terminated prematurely due to arked hyperglycemia In 58 per cent (36/62) of e patients the serum osmolarity was normal d in 39 per cent (29/62) it was mildly depressed 67 279 mOsm per liter)

Hyperkalemia Hyperkalemia was the most equent and most potentially life threatening omplication encountered Peak serum potassium uring GIK infusion averaged 5 1 ± 0 1 mEq per ter however serum potassium levels of > 6 0 mEq per liter during GIK infusion were observed n seven of the 70 patients all of whom had either ltered renal function or diabetes or both

In 21 patients in whom the serum potassium was monitored serially for 48 hours after GIK infusion potassium levels of 6 0 mEq per liter or greater were detected in 38 per cent (8/21) all but one of whom had altered renal function or diabetes. Mean serum potassium after infusion (5.8 ± 0 2 mEq per liter) was significantly greater ($p < 0\ 0005$) than mean serum potassium during GIK infusion (4 5 ± 0 1 mEq per liter)

Severe hyperkalemia was managed by adminis tration of sodium polystyrene sulfonate (Kayex alate) and by reducing the KCl content of the GIK infusate In general the hyperkalemia was clinically well tolerated without ECG evidence of QRS widening heart block or other toxic mani festations However one GIK recipient (patient No 6 Table IV) died in cardiogenic shock while hyperkalemic (K 7 0 mEq per liter) 12 hours following discontinuation of his 48 hour course of GIK Prior to GIK infusion this patient had sustained cardiac arrest at home prolonged cere bral anoxia and flail chest following cardiopul monary resuscitation by paramedical personnel During his entire hospital course he was coma tose respirator dependent and markedly oligu ric Whether hyperkalemia contributed to his death is uncertain particularly since his ECG terminally showed no hyperkalemic manifesta tions

Pulmonary venous hypertension Pathological elevation of the pulmonary artery end-diastolic pressure (PAEDP) used as an estimate of left ventricular filling pressure[3] was not generally a problem during GIK infusion In only one patient was GIK discontinued prematurely because of elevated PAEDP (28 mm Hg) In this patient the

Table IV Prognostic index scores and extent of coronary artery disease in nonsurvivors

Pt No	Age	Sex	MI site	Prognostic index scores: Killip	Peel	Norris	Hours lived	Hem mon†	Number of coronary arteries > 50% stenosis
GIK group (n = 11)									
1	58	M	I	2	20	9.42	52	+	[illegible]
2	63	M	A	4	27	12.84	2	+	3
3	69	M	A	4	23	10.52	2	+	3
4	57	M	A	4	22	9.75	24	+	3
5	52	F	A	1	27	13.56	60	+	U
6	61	M	I	2	21	6.70	60	+	2
7	58	M	A	3	16	11.56	96	+	3
8	58	M	A	4	18	11.66	24	+	3
9	72	F	I	1	18	10.18	34	+	U
10	59	M	A	4	26	12.81	434	+	3
11	64	F	A	2	17	8.54	144	+	1
Mean	61			3.4	21	10.7	85		
± SEM	2			0.3	1	0.6	37		
Control group (n = 19)									
1	58	M	I	1	11	5.42	4	0	U
2	67	M	I	1	13	4.70	29	0	[illegible]
3	58	M	A	2	14	5.86	106	0	2
4	75	F	A	2	15	5.92	6	0	1
5	79	F	I	2	14	5.48	68	0	3
6	57	M	A	2	10	7.76	19	+	3
7	76	M	A	2	21	6.32	53	0	3
8	80	M	I	2	18	9.26	5	0	U
9	53	F	A	2	17	9.25	26	+	U
10	65	F	I	3	17	10.00	250	+	3
11	69	M	A	3	14	8.62	46	0	2
12	36	F	I	4	18	5.14	73	+	[illegible]
13	59	M	U	4	26	6.96	23	+	3
14	72	M	U	4	26	8.06	262	+	3
15	58	F	A	4	27	10.25	6	+	3
16	81	F	I	4	22	15.86	2	0	1
17	67	F	A	4	22	12.14	215	+	2
18	83	M	I	4	22	13.91	12	+	[illegible]
19	60	M	A	4	27	12.03	44	+	U
Mean	66			2.8	19	8.6	68		
± SEM	3			0.3	1	0.7	21		
P	NS‡			NS	NS	0.056	NS		

A = anterior I = inferior U = undetermined
†Hem mon = invasive hemodynamic monitoring performed + = yes 0 = no
‡NS = not significant (p > 0.10)

site reported by others[3,5] as a complication of intravenous GIK infusion was not observed in our series presumably because the GIK was delivered directly into the right atrium

Hyperglycemia Peak glucose during GIK infusion averaged 286 ± 17 mg per 100 ml in the 70 patients Supplemental subcutaneous or intravenous regular insulin was required for management of hyperglycemia in 10 of the 16 diabetic and in nine of the 54 nondiabetic GIK recipients

Marked hyperglycemia (glucose > 350 mg per 100 ml) was noted in 13 patients, eight of whom were diabetic In two of these patients both insulin dependent serum glucose rose to levels exceeding 650 mg per 100 ml despite supplemental insulin requiring the GIK infusion to be terminated prematurely Asymptomatic and clinically inapparent hypoglycemia was discovered in one patient (glucose 45 mg per 100 ml) during GIK infusion

ugh an excellent metabolic substrate under ic conditions FFA may not be the optimum rate for the ischemic myocardium along the ry of the central core of irreversibly cted tissue Unlike glucose FFA cannot be bolized anaerobically furthermore the aer tabolism of FFA requires slightly more en per unit of energy yield than does se [1,2] FFA have been shown experimen to increase myocardial oxygen consump [21,22] to reduce myocardial mechanical per ance in the setting of hypoxia [23] and to be ythmogenic [1,2] although this latter point dispute [5,24] Glucose on the other hand does ly undergo anaerobic metabolism (glycoly It has been estimated that glycolysis might ble to transiently support ischemic tissue on periphery of an infarct especially if that e has reduced contractility

lucose insulin infusions will not only stimu e myocardial carbohydrate metabolism [1] but also reduce the availability of FFA the latter stimulation of FFA esterification and via ibition of lipolysis Thus by increasing h aerobic and anaerobic glucose metabolism d by decreasing FFA availability GIK solu ns could theoretically reduce myocardial ygen demands [1] and perhaps improve myocar al viability and performance

Rationale for current GIK regimen On the pothesis that GIK might reduce infarct size d mortality rate through suppression of FFA e sought a regimen which would suppress FFA r patients with acute myocardial infarction to bthreshold levels (< 300 μEq per liter) Studies ormed in our laboratory on fasting pain free tients with stable coronary artery disease have ently demonstrated that arterial coronary ous differences of FFA were zero when GIK (300 m of glucose 50 U of regular insulin and 80 Eq of KCl per liter of H_2O) was infused at rates ≥ 1.5 ml per kilogram per hour In our initial udies with GIK infusion in patients with acute yocardial infarction quantities of GIK less han 1.5 ml per kilogram per hour were not found o produce consistent reduction of FFA espe ially during episodes of chest pain when FFA ould often rise abruptly Increasing the infusion ate to 1.5 ml per kilogram per hour suppressed FA to subthreshold levels in both the presence and the absence of pain [8]

Fig 1 shows that in the present study FFA were dramatically reduced in every patient in whom FFA were initially elevated In most cases FFA were reduced to subthreshold levels The importance of the infusion rate is shown in Fig 2 The optimal infusion rate for consistent FFA suppression would appear again to be ≥ 1 5 ml per kilogram per hour—this amounts to an hourly dosage of 31 5 Gm of glucose, 5 2 U of insulin and 8 4 mEq of KCl in a 70 kilogram subject These dosages are approximately 4 to 5 times the quantities originally administered by earlier investigators [6] (Table V)

Mortality data Comparison of the mortality rates of the GIK treated patients and controls shows a reduction in the over all hospital mortality rate in the treated group of 47 per cent ($p < 0.05$) When the severity of infarction in each patient was assessed by the prognostic indices of Killip Peel and Norris respectively it was discovered that the mortality rate of the controls was not significantly different from that predicted by the prognostic indices The mortality rate of the GIK recipients was however significantly reduced by 42 50 and 35 per cent in the Killip Peel and Norris predictions respectively

It should be acknowledged that the GIK recipients were not a consecutive series and furthermore that the mean age of the GIK group was significantly less than that of the control group otherwise the two patient populations were remarkably well matched by clinical criteria The nonconsecutive state of the GIK group was in general chiefly dictated by technical and logistical problems i e the inability to hemodynamically monitor simultaneously multiple patients and in no way represented an attempt to restrict GIK administration to uncomplicated infarcts Indeed the great similarity between the magnitude of the mean prognostic scores of the GIK and control populations calculated independently by the methods of Killip Peel and Norris further testifies to the similarity of the GIK and control groups

Study of the GIK patient deaths (Table IV Fig 6) reveals that there were no deaths in patients having single vessel coronary artery disease few deaths in those with two vessel disease and also few deaths in patients having no history of prior myocardial infarction These facts would support the thesis that if GIK is to provide metabolic support it must do so via perfusion of

Table V Comparison of reported clinical and laboratory trials with intravenous GIK infusion

Study	No pts (GIK/total)	Elapsed time since infarct (hours)	Maximum concentration: Glu gm%	Ins U/L	K mEq/L	Maximum infusion rate: Glu Gm/hr	Ins U/hr	K mEq/hr	Hours infused	Vol cc/hr (ml)	Re[illegible]
Sodi Pallares et al 1963	25/50		10	20	40	6.3	1.2	2.5	?168	60	+
Mittra 1965‡	85/170	Mean 22 hr	10	20	40	8.3	1.7	3.3	336	53	+
Pentecost et al 1968	100/200	90 ≤ 24 hr	10	50	50	6.3	1.9	1.9	48	[illegible]	0
Fletcher et al 1968	16/60		10	40	80	4.2	1.7	3.3	72	42	0
Medical Research Council 1968‡	410/840	66 ≤ 24 hr	10	20	30	6.3	1.2	1.9	336	63	0
Maroko et al 1972	14/37 (dogs)	½ hr	50	102	210	22.5	4.6	9.5	24	45	
Lesch et al 1974	8/18	Pacing study	50	60	200	75.0	9.0	30.0	1	150	0
Parker et al 1974	11/11	Pacing study	20	40	80	48.0	9.6	19.2	3/4	240	+
Present study 1976§	70/134	Mean 8 hr	30	50	80	31.5	5.2	9.4	48	105	+

Glu = glucose Ins = insulin K = potassium
†+ = beneficial effect of GIK shown in study 0 = no beneficial effect shown
‡Study in which GIK was preferentially administered orally (with subcutaneous insulin) to most patients rather than intravenously
§Data from present study calculated for 70 kilogram subject at infusion rate of 1.5 ml per kilogram per hour

GIK infusion was restarted 8 hours later following diuresis, and continued uninterrupted for another 48 hours In general the PAEDP was found to fall slightly during the 48 hour course of GIK infusion as has often been observed in patients with acute myocardial infarction who are hemodynamically monitored [36]

Discussion

Historical perspective Numerous investigators have evaluated the effects of intravenous glucose insulin potassium infusion as a treatment for ischemic heart disease since the concept was introduced by Sodi Pallares and associates [1,2] The design and results of several selected studies are presented in Table V It is clearly evident that these reported studies differed widely in the concentrations of the glucose insulin and potassium infused and in the volume and duration of the infusion Few studies limited their population to patients with infarcts < 15 hours in age Two of the largest studies[3,6] administered GIK preferentially as an oral regimen of glucose and potassium along with subcutaneous insulin rather than using the intravenous route Several of the more recent clinical and laboratory studies including the present one have utilized much higher infusion rates of glucose insulin and potassium than originally advocated by Sodi Pallares

Theoretical benefits of GIK infusion Although initially proposed by Sodi Pallares and associates[1,2] as a polarizing solution to prevent arrhythmias and further ischemic damage by repletion of intracellular potassium in ischemic cells, GIK may exert its maximal beneficial effects via other routes Such potential benefits of GIK infusion might include the stabilization of cellular membrane potential,[40] the enhancement of glycolytic energy production,[9] and the enhancement of contractility by a hyperosmolarity effect [41] However it is possible that the greatest benefit of GIK lies in its ability to suppress free fatty acids

Myocardial substrate interactions Under aerobic conditions the predominant myocardial energy substrate in the fasting state is lipid (FFA) [42,43] FFA are extracted in direct proportion to their arterial concentration[44,45] and are not extracted when arterial FFA falls below 350 µEq per liter the arterial threshold for FFA [46] FFA metabolism furthermore has an inhibitory effect on glycolysis[47,48] and conversely carbohydrate intake suppresses myocardial FFA metabolism [43,47,49]

In the setting of myocardial ischemia drastic alterations in cardiac metabolism may occur Serum FFA levels are markedly elevated[50,51] probably secondary to release of norepinephrine and reduction of serum insulin levels.[52]

tion the mortality rate was reduced four n GIK recipients compared to controls (6 vs r cent $p < 0.05$) Complications of GIK ion were infrequent and included chiefly glycemia and hyperkalemia both of which ted meticulous monitoring of serum chemis

e data suggest that suppression of plasma with GIK infusion may be associated with a ficant reduction in the hospital mortality of acute myocardial infarction

e authors gratefully acknowledge the statistical analysis r John Burdeshaw the secretarial assistance of Mrs D Smith and Mrs Katherine T Young and the helpful stions of Drs Robert A Kriesberg and Lloyd L Hefner g the course of this investigation

RENCES

Sodi Pallares, D Testelli, M R Fishleder [redacted] L, Bisteni, A Medrano G A Friedland C and De Micheli, A. Effects of an intravenous infusion of a potassium glucose insulin solution on the electrocardiographic signs of myocardial infarction Am J Cardiol 9 166 1962

Sodi Pallares, D Bisteni A Medrano C A Testelli M. R and De Micheli A The polarizing treatment of acute myocardial infarction Dis Chest 43 424 1963

Mittra B Potassium glucose and insulin in treatment of myocardial infarction Lancet 2 607 1965

Pentecost, B L. Mayne N M C and Lamb P Controlled trial of intravenous glucose potassium and insulin in acute myocardial infarction Lancet 1 946 1968

Fletcher G F Hurst J W and Schlant R C "Polarizing solutions in patients with acute myocardial infarction, Am Heart J 75 319 1968

Medical Research Council Working Party on the Treatment of Myocardial Infarction Potassium glucose and insulin treatment for acute myocardial infarction Lancet 2 1355 1968

Brachfeld, N The glucose insulin potassium (GIK) regimen in the treatment of myocardial ischemia Circulation 48 459 1973

Oliver M F Glucose insulin potassium in acute myocardial infarction Acta Cardiol Suppl. 17 257 1973

Opie, L. H. The glucose hypothesis relation to acute myocardial ischaemia J Mol Cell Cardiol 1 107 1970

Gupta D K Jewitt D E Young R Hartog M and Opie L. H Increased plasma free-fatty acid concentrations and their significance in patients with acute myocardial infarction Lancet 2 1209 1969

Oliver M. F Kurien V A and Vetter N Metabolic intervention, in Oliver [redacted] F Julian D G and Donald K. W editors Effect of acute ischemia on myocardial function Baltimore 1972, The Williams & Wilkins Company p. 364

2. Stanley A. W Jr Russell, [redacted] O Jr McDaniel H G., and Rackley C F Glucose insulin potassium free fatty acids, pain and the acute myocardial infarction Clin Res. [redacted] 57A (abst) 1974

13. Kurien, V A., and Oliver M F Serum free-fatty acids after acute myocardial infarction and cerebral vascular occlusion Lancet 2 122 1966.

14 Allison S P Chamberlain [redacted] J and Hinton [redacted] Intravenous glucose tolerance insulin glucose and free fatty acid levels after myocardial infarction Br Med J 4 776 1969

15 Rutenberg, H. L. Pamintuan J C., and Soloff L. A Serum free fatty acids and their relation to complications after acute myocardial infarction Lancet 2 559 1969

16 Januszewicz W Sznajderman M Ciswicka Sznajderman M. Wocial B., and Rymaszewski, Z. Plasma free fatty and and catecholamine levels in patients with acute myocardial infarction Br Heart J [redacted] 716 1971

17 Vetter N J Adams W., Strange R C., and Oliver M F Initial metabolic and hormonal response to acute myocardial infarction Lancet 1 284 1974

18 Oliver M. [redacted] Kurien V A., and Greenwood T W Relation between serum free fatty acids and arrhythmias and death after acute myocardial infarction Lancet 1 710 1968

19 Kurien V A and Oliver M F A metabolic cause for arrhythmias during acute myocardial hypoxia Lancet 1 813 1970

20 Kurien V A. Yates, P A and Oliver M F The role of free fatty acids in the production of ventricular arrhythmias after acute coronary artery occlusion Eur J Clin Invest 1 225 1971

21 Challoner D R. and Steinberg D Effect of free fatty acid on the oxygen consumption of perfused rat heart Am J Physiol. 210 280 1966

22 Mjøs O D Effect of free fatty acids on myocardial function and oxygen consumption in intact dogs, J Clin. Invest 50 1386 1971

23 Severed L. Connor W E and Long J P The depressant effect of fatty acids on the isolated rabbit heart Proc. Soc Exp Biol. Med 131 1239 1969

24 Henderson, A H Most, A. S Parmley W W., Gorlin R. and Sonnenblick, [redacted] H Depression of myocardial contractility in rats by free fatty acids during hypoxia Circ Res. 26 439 1970

25 Kjekshus J K and Mjøs, O D Effect of free fatty acids on myocardial function and metabolism in the ischemic dog heart J Clin Invest 51 1767 1972.

26 Carlsten A Hallgren, B Jagenburg R., Svanborg A and Werko L. Myocardial arteriovenous differences of individual free fatty acids in healthy human individuals Metabolism 12 1063 1963

27 Killip T., and Kimball J T Treatment of myocardial infarction in a coronary care unit, Am J Cardiol. 20 457 1967

28 Peel, A. A F Semple T Wang I Lancaster W M and Dall, J L. G A coronary prognostic index for grading the severity of infarction Br Heart J 24 745 196

29 Norris, R. M Brandt, P W T Caughey D E Lee A. J and Scott P J A new coronary prognostic index Lancet 1 274 1969

30 Dowling, J T Russell, R O Jr Massing G K and Rackley C F Present-day management of acute myocardial infarction South Med. J 66 518 1973

31 Duncombe W G The colorimetric micro determination of nonesterified fatty acids in plasma Clin Chim. Acta 9 122 1964

32 Korn, E. D Clearing factor a heparin activated lipoprotein lipase J Biol. Chem 215 1 1955

33 Rutstein D D Castelli, W P and Nickerson R J Heparin and human lipid metabolism, Lancet 1 1003 1969

34 Rogers, W J Stanley A. W Russell, R O Jr Moraski

ischemic tissue Perfusion would be most difficult, if not impossible in patients with severe two and three vessel coronary artery disease this group would also likely include most patients with history of prior myocardial infarction On the other hand patients with single vessel disease would receive maximal benefit through perfusion of ischemic areas via the uninvolved vessels and collateral channels

Complications of GIK administration Despite the encouraging mortality statistics presented above, the GIK infusion was not without complications, especially in patients with altered renal function or diabetes Although the major complications, hyperglycemia and hyperkalemia were easily managed in most patients one hyperkalemic oliguric patient died in cardiogenic shock several hours following discontinuation of his course of GIK Hyperkalemia in this patient could not be definitely incriminated as the cause of death however, since no ECG evidence of potassium toxicity was evident Two insulin dependent diabetic patients had marked hyperglycemia and hyperosmolarity during GIK infusion not responsive to supplemental insulin necessitating premature termination of their GIK infusion

Guidelines for GIK administration Because of these observed complications we currently feel that GIK administration though potentially of great benefit in the early postinfarct period is still in the investigative stage awaiting further controlled clinical trials and not yet ready for utilization by the community hospital Our data would suggest that an infusion of 1 5 ml per kilogram per hour of the previously defined GIK solution would appear optimum to suppress FFA to subthreshold levels Patients receiving GIK should be serially monitored with serum glucose electrolytes and PAEDP or pulmonary capillary wedge pressure Serum potassium should be monitored for 24 to 48 hours following GIK discontinuation, since this is the period of maximum serum potassium levels Hyperkalemia should be treated by reduction of potassium in the infusate as proposed by Sodi Pallares and associates[64] and, if necessary by administration of sodium polystyrene sulfonate (Kayexalate) Hyperglycemia should be managed with supplemental insulin

In conclusion this study demonstrates that patients with acute myocardial infarction can be routinely instrumented and begun on a metab support regimen within 15 hours (mean 8 hours) of onset of chest pain The data sug that metabolic intervention with glucose potassium in dosage sufficient to reduce free f acid levels to subthreshold may favora influence the hospital mortality rate of ac myocardial infarction Patients most likely t benefit from the GIK infusion would seem to b those without history of prior infarction and wi relatively uncomplicated clinical presentat The GIK infusion is not without complicat and meticulous attention to serum glucose potassium is necessary during and immediate following discontinuance of GIK, especially in patients with diabetes or altered renal funct Additional controlled clinical studies would se indicated to further investigate the efficacy of metabolic support of acute myocardial infarctio with GIK, and to further elucidate its mechan of action and its effects on myocardial electri stability and mechanical performance

Summary

Free fatty acids (FFA) the predomina myocardial energy substrate, are present in increased quantities immediately following acu myocardial infarction (AMI) and may cause deleterious alterations in cardiac rhythm, oxyg consumption, and mechanical performance In an attempt to suppress FFA and simultaneou increase the availability of carbohydrate as myocardial substrate 70 patients with unequi ocal AMI were administered a right atrial infusion of glucose insulin potassium (GIK) (3 Gm of glucose 50 U of regular insulin and mEq of KCl per liter of H_2O) at a constant rate of 0 5 to 2 0 ml per kilogram per hour for 48 hours A dramatic fall in FFA (944 ± 57 to 289 ± 16 μEq per liter p < 0 0005) occurred during GIK infusion and FFA rebounded to 420 ± 39 μEq per liter (p < 0 005) when GIK was discontinued

The hospital mortality rate in the 70 GIK recipients was compared to that of 64 untreated patients (controls) from the same coronary care unit during the previous year GIK and control groups had similar severity of infarction as assessed by prognostic scales of Killip, Peel and Norris respectively The hospital mortality rate was reduced in the GIK recipients compared to the control group (11/70 vs 19/64 p < 0 05) In patients without history of prior myocardial

ᶠcts of ısosorbıde dınıtrate and nıtroglycerın on central ˈulatory dynamıcs ın coronary artery dısease

_us J Battock M D
W Levıtt M D
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r Colo

_ough sublıngual nıtroglycerın ıs the prımary t for the treatment of acute attacks of angına ons the use of long actıng nıtrate prepara s remaıns controversıal as to theır effectıve as prophylactıc agents agaınst the precıpıta of angınal attacks In addıtıon nıtrate apy has more recently been used to ımprove trıcular functıon ın patıents wıth congestıve rt faılure As thıs mode of therapy ıs omıng wıdely accepted both ın the treatment acute myocardıal ınfarctıon and left ventrıc dysfunctıon ıt ıs ımperatıve that the nature duratıon of the hemodynamıc responses be ıned

he purpose of thıs paper ıs to compare the e and duratıon of effects of sublıngual nıtro cerın to sublıngual and oral ısosorbıde dını te on central cırculatory dynamıcs ın patıents h stable chronıc coronary artery dısease

ethods

Twenty seven men wıth angıographıcally oved coronary artery dısease (>50 per cent struction of at least one major coronary vessel) us a hıstory of angına were evaluated ın the stıng state after beıng off all nıtrate prepara ons for at least 48 hours Other cardıac medıca ons such as dıgıtalıs propranolol or dıuretıcs ere not altered Central cırculatory dynamıcs ere measured wıth a radıonuclıde technıque fter ınsertıon of a central venous catheter ınto e superıor vena cava the mıdpoınt of the left ventrıcle was marked on the chest wall under fluoroscopy ın the supıne anteroposterıor posıtıon Wıth the use of quantıtatıve radıocardıography a bolus of ¹¹³ᵐIndıum (approxımately 1 mc) was ınjected ınto the superıor vena cava and by use of a collımated, sıngle scıntıllatıon probe located over the mıdpoınt of the left ventrıcle a tracıng of the passage of ısotope through the rıght ventrıcle lungs and left ventrıcle was recorded on a strıp chart recorder (Fıg 1)[1] After 5 mınutes count rate at equılıbrıum was recorded and then a background record was obtaıned whıch reflected counts from surroundıng tıssues after eclıpsıng the left ventrıcle[1] Left ventrıcular ejectıon fractıon was calculated from the background corrected tıme actıvıty curve as the fractıonal fall ın count rate related to the end dıastolıc count rate Sınce ¹¹³ᵐIndıum bınds to

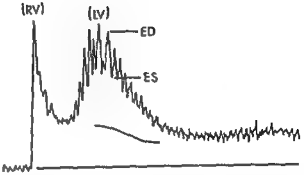

Fıg 1 Precordıal hıgh frequency radıocardıogram (tıme actıvıty curve) recorded followıng ınjectıon of ¹¹³ᵐIndıum ınto the superıor vena cava The rıght ventrıcular (*RV*) and left ventrıcular (*LV*) peaks are ıdentıfıed and the eclıpse trace ıs the solıd lıne beneath the left ventrıcular portıon of the curve Left ventrıcular ejectıon fractıon ıs calculated as the fractıonal fall ın count rate from end dıastole (*ED*) to end systole (*ES*) dıvıded by the corrected end dıastolıc count rate (*ED* eclıpse count rate) Ejectıon fractıon ıs 0 49 for the beat marked (*ED ES*) and 0 42 0 44 0 44 respectıvely for the next 3 beats (average of 4 beats = 0 45)

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R E McDaniel H G and Rackley C E Heparin induced free fatty acid elevation in patients with coronary artery disease Clin Res 23 8A (abst), 1975

35 Stanley A W Jr Willis W H Jr Kreisberg R A Russell R O Jr and Rackley C E Pulmonary infiltration with glucose insulin potassium infusion during acute myocardial infarction Clin Res 21 452 (abst) 1973

36 Russell R O Jr and Rackley C E Hemodynamic monitoring in a coronary intensive care unit Mount Kisco 1974 Futura Publishing Company

37 Maroko P R Libby P Sobel B E Bloor C M Sybers, H D Shell W E Covell J W and Braunwald E Effect of glucose insulin potassium infusion on myocardial infarction following experimental coronary artery occlusion Circulation 45 1160 1972

38 Lesch M Teichholz, L E Soeldner J S and Corlin, R Ineffectiveness of glucose potassium and insulin infusion during pacing stress in chronic ischemic heart disease Circulation 49 1028 1974

39 Parker J O Manmohansingh P R Steele R J Walker D M West R O and Chiong M A The protective effect of glucose insulin potassium on the response to atrial pacing Circulation 49—50 Suppl III 34 (abst) 1974

40 MacLeod D P and Daniel E E Influence of glucose on the transmembrane action potential of anoxic papillary muscle J Gen Physiol 48 887 1965

41 Wildenthal K Mierzwiak D S and Mitchell J H Acute effects of increased serum osmolality on left ventricular performance Am J Physiol 216 898 1969

42 Bing R J Siegal A Ungar I and Gilbert M Metabolism of the human heart Am J Med 16 504 1954

43 Gordon R S and Cherkes A Unesterified fatty acid in human blood plasma J Clin Invest 35 206 1956

44 Carlsten A Hallgren B Jagenburg R Svanborg A and Werko L Myocardial metabolism of glucose lactic acid amino acids and fatty acids in healthy human individuals at rest and at different work loads Scand J Clin Lab Invest 13 418 1961

45 Ballard F B Danforth W H Naegle S and Bing R J Myocardial metabolism of fatty acids J Clin Invest 39 717 1960

46 Scott J C Finkelstein L J and Spitzer J J Myocardial removal of free fatty acids under normal and pathological conditions Am J Physiol 203 482 1962

47 Randle P J Garland P B Hales C N and Newsholme E A The glucose fatty acid cycle Lancet 1 785 1963

48 Wahlqvist M L Carlson L A Eklund B Kaijser L Lassers B W Low H Nye E R and Rossner S Substrate competition in human myocardial metabolism Adv Cardiol 12 94 1974

49 Bing R J Siegel A Vitale A Balboni, F Sparks, E Taeschler M Klapper M and Edwards, S Metabolic studies on the human heart in vivo Am J Med 15 ... 1953

50 Christensen N J, and Videbaek J Plasma catecholamines and carbohydrate metabolism in patients with acute myocardial infarction J Clin Invest 54 ... 1974

51 Documenta Geigy In Diem K editor Scientific tables Ardsley N Y 1962 Geigy Pharmaceuticals, p 6...

52 Opie L H Myocardial energy metabolism, Adv Cardiol 12 70 1974

53 Russo, J V Margolis S Friesinger G C and Ross, R S Heparin and ventricular arrhythmias after myocardial infarction Lancet 2 1271 19...

54 Nelson P G Effect of heparin on serum free-fatty acids, plasma catecholamines and the incidence of arrhythmias following acute myocardial infarction Br Med J 3 735 1970

55 Opie L H Thomas M Owen P Norris R M Holland A. J., and Van Noorden S Failure of high concentrations of circulating free fatty acids to provoke arrhythmias in experimental myocardial infarction Lancet 1 818 1971

56 Hagenfeldt L and Wester P O Plasma levels of individual free fatty acids in patients with acute myocardial infarction Acta Med Scand 194 357 19...

57 Opie L H Metabolic response during impending myocardial infarction Circulation 45 483 1972

58 Gordon R S and Cherkes, A Production of unesterified fatty acids from isolated rat adipose tissue incubated in vitro Proc Soc Exp Biol Med. 97 150, 1...

59 Bally P R Cahill C F Leboeuf B and Renold, A E Studies on rat adipose tissue in vitro J Biol Chem 235 333 1960

60 Raben M S and Hollenberg C H Effect of ... and insulin on the esterification of fatty acids by isolated adipose tissue J Clin Invest 39 435 1960

61 Haneda T Ganz, W Lee T and Katz, J Reduction of myocardial oxygen demand by glucose insulin potassium (CIK) Circulation 49 50 Suppl III 102 (abst.) 1...

62 Amsterdam E A Foley D Massumi, A Zelis, R and Mason D T Enhancement of myocardial function during hypoxia by increased glucose availability Am J Cardiol 29 251 (abst) 1972

63 Stanley A W Jr Moraski R E and Russell R O Jr Rogers, W J Mantle J A Kreisberg R A McDaniel H G and Rackley C E Effects of glucose insulin potassium on myocardial substrate availability and utilization Am J Cardiol in press.

64 Sodi Pallares D Ponce de Leon J Bisteni, A and Medrano G A Potassium glucose and insulin in myocardial infarction Lancet 1 1315 1969

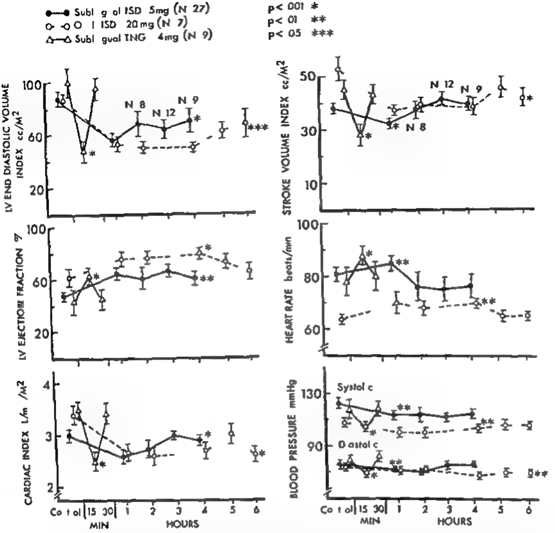

Fig 2 Effects of nitroglycerin and isosorbide dinitrate on central circulatory dynamics Error bars represent standard errors of the mean The indicates the last point where the value was significantly different from control and is also indicative that all prior values were of same significance Abbreviations are the same as in Table I

ficantly different from control after 1 hour significant changes in LVEDVI ($p < 0.001$) F ($p < 0.05$) and CI ($p < 0.001$) were still ...nt 4 hours following drug administration ISD on the other hand produced significant ...ges in all parameters at 4 hours with persist... changes in LVEDVI ($p < 0.05$) CI ($p < 0.001$) and SVI ($p < 0.001$) at 6 hours after ... ingestion

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...he results presented suggest that nitrates ...t central circulatory dynamics by altering ... preload and afterload Earlier studies have ...wn a reduction in left ventricular filling pres... by nitroglycerin and oral ISD as well as a decrease in ventricular dimensions by nitroglycerin Our studies have shown a definite reduction in LVEDVI and SVI that support this work The results show an increase in heart rate which is most likely a reflex response to the decrease in stroke volume in an attempt by the cardiovascular system to maintain cardiac output Of interest is that there was an increase in left ventricular ejection fraction after nitrate administration Whether this represents a response to a decreased stroke volume or is a primary increase in left ventricular contractility cannot be stated from the present study Cardiac index was regularly reduced by nitrate administration an effect recently demonstrated with oral ISD[1] This may be due to a greater reduction of left ventricular

Table I Comparison of significant changes in central circulatory dynamics by nitroglycerin and isosorbide dinitrate

Parameter	SEM	Sublingual TNG (N = 9)		Sublingual ISD (N = 27)		Oral ISD (N = [illegible])	
		Control	15 minutes	Control	1 hour	Control	[illegible]
LV end diastolic volume index (c c /M²)		100	47	88	56	87	[illegible]
	±	11 0	8 9	5 9	4 4	4 5	[illegible]
LV ejection fraction (%)		43	63	48	65	62	[illegible]
	±	9 2	6 7	3 1	4 2	6 1	[illegible]
Cardiac index (L /min /M²)		3 5	2 5	3 0	2 6	3 4	[illegible]
	±	0 18	0 17	0 12	0 12	0 16	
Stroke volume index (c c / M²)		45	28	38	32	53	[illegible]
	±	3 8	4 0	1 8	1 8	4 1	[illegible]
Heart rate (beats/min)		79	84	81	85	64	[illegible]
	±	5 1	3 0	2 2	2 7	0 57	[illegible]
Blood pressure (mm Hg)		118/80	105/70	123/76	114/72	108/74	[illegible]
	±	2 1/2 2	5 3/2 0	3 2/2 9	1 4/1 4	2 4/2 2	[illegible]

TNG Nitroglycerin ISD isosorbide dinitrate LV left ventricular SEM standard error of the mean N number of patients
All values p < 0 001 except those marked (p < 0 01)

plasma transferrin, blood volume and cardiac output could be measured All of these parameters have previously been shown to correlate well with standard methods [14] Arterial blood pressure and heart rate were measured at the time of initial injection of isotope Stroke volume was calculated as cardiac output/heart rate and left ventricular end diastolic volume as stroke volume/ejection fraction Thus, the following parameters of central circulatory dynamics were measured in all patients before and after drug therapy Heart rate (HR) blood pressure (BP) cardiac index (CI) stroke volume index (SVI) left ventricular end diastolic volume index (LVEDVI), and left ventricular ejection fraction (LVEF)

After the initial measurements patients were immediately given either 0 4 mg of sublingual (SL) nitroglycerin (TNG) (nine patients) 5 mg of SL isosorbide dinitrate (ISD) (27 patients) or 20 mg of oral ISD (seven patients) and serial measurements of central circulatory dynamics were made for 30 minutes after SL TNG for 4 hours after SL ISD and for 6 hours after oral ISD Statistical analysis of the results was done by using Student s paired t test

Results

Table I compares the mean values and standard errors of the mean in the three groups of patients The nine patients who received T were also studied at 5 minutes after drug ad istration and had values virtually identical those observed at 15 minutes Twenty two of 27 patients who received SL ISD were stud 15 minutes again with the values being similar to the 1 hour values It can be seen th all groups there was a significant (p < 0 00 p < 0 01) decrease in LVEDVI CI, SVI and with a concomitant increase in LVEF and with the changes being similar at 15 minutes SL TNG 1 hour after SL ISD and 4 ho rs oral ISD Two patients were studied up to 6 h on placebo with no significant changes in a the measured parameters

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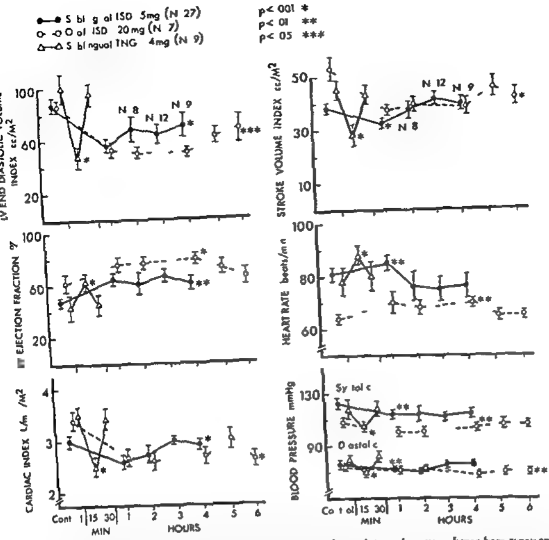

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Fig 2 depicts the time changes in central circulatory dynamics by these same drugs Of the 27 patients receiving SL ISD eight were followed for 2 hours 12 for 3 hours and nine until 4 hours after administration of drug The varied number of patients after 1 hour are accounted for by several patients being evaluated at only two of the three hourly periods The control values in these subgroups differed slightly from the control value shown for the 27 patients but the levels of significance were based on the difference from the acutal control values (paired) for these patients

In the TNG group all values returned to control by 30 minutes after administration In the SL ISD [illegible] CI, HR and BP were [illegible]

parison of the effects of atrial and ventricular ulation on sinus node function in man

Bissett M D
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ature ventricular beats usually do not reset sinus pacemaker and the ensuing pause is compensatory The compensatory pause result from lack of retrograde conduction the ventricle to the atrium however both cal and experimental observations have an that ventriculoatrial conduction ■ a mon occurrence in man[1, 2] The lack of sinus al reset may then result from inappropriate ing of the retrograde atrial impulse or retro de atriosinus block The purpose of this study to investigate the production of compensa y and noncompensatory pauses by premature tricular contractions (PVC s) through a com rison of the effects of atrial and ventricular mulation on sinus node function

thods

Electrophysiologic studies were completed in patients with a mean age of 50 ± 8 years dergoing diagnostic cardiac catheterization for aluation of chest pain No patient was receiving ugs known to affect sinus node function After formed consent had been obtained the patients ere brought to the cardiac catheterization labo atory in the nonsedated postabsorptive state His bundle electrograms were obtained by stan ard catheter technique and a quadripolar cath ter was positioned in the high right atrium for atrial pacing and recording of the atrial electro gram A bipolar catheter was positioned in the right ventricular apex for ventricular stimula tion

During sinus rhythm a digital programmed stimulator[4] was used to apply a premature atrial stimulus at 10 msec intervals throughout the cardiac cycle after every eighth sinus beat Following completion of premature atrial stimu lation PVC s were elicited by programmed stim ulation at 10 msec intervals through the cardiac cycle up to the termination of the T wave of the preceding sinus beat Current was delivered by a Tektronix stimulus isolation box at a value slightly above diastolic threshold Simultaneous recordings of electrocardiographic (ECG) Leads I II III and V with the His bundle electrogram and high atrial electrogram were recorded on a multichannel oscilloscope recorder (Figs 1 and 2)

The interval between the last sinus beat (A1) and atrial depolarization (A2) produced by premature atrial stimuli or retrograde from premature ventricular stimuli (A1 A2 interval) was utilized to measure the zone of sinus node reset or nonreset When the pause following atrial stimulation was fully compensatory that is A1 A2 plus the interval between the PAC (A2) and the next spontaneous sinus beat (A3) equalled twice the sinus cycle length (A1 A1) the sinus node was not reset[5, 6] When the pause from the atrial premature (antegrade or retrograde) was followed by a less than compensatory pause and A1 A2 plus A2 A3 was less than two times the sinus cycle length (A1 A1) sinus node reset was said to occur[5, 6] In each case the mean sinus cycle

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preload than the effects on heart rate and blood pressure but did not seem to be clinically deleterious at least in these patients with stable coronary artery disease In contrast in patients with cardiomyopathy in whom this reduction could potentially be hazardous this effect of nitrates was not seen and in fact ISD increased abnormally reduced cardiac index in these patients[13]

Although Goldstein and Epstein have stated that there may not be a relationship between the hemodynamic effects of nitrates and therapeutic benefit of nitrates in the relief of angina it is clear that the increased duration of these hemodynamic effects with isosorbide dinitrate as compared to nitroglycerin is convenient particularly when nitrates are being used in acute myocardial infarction and treatment of congestive heart failure This study in agreement with others, demonstrates that nitrates affect both left ventricular preload and afterload The durations of both sublingual and oral ISD are longer than TNG and act as long as 4 and 6 hours respectively

Summary

This study compares the effects and duration of the effects of 5 mg of sublingual (SL) isosorbide dinitrate (ISD) 20 mg of oral ISD and 0 4 mg of SL nitroglycerin (TNG) on central circulatory dynamics Twenty seven patients with coronary artery disease were evaluated with radioisotope techniques and determinations made of heart rate (HR) blood pressure (BP) cardiac index (CI) stroke volume index (SVI) left ventricular end diastolic volume index (LVEDVI) and left ventricular ejection fraction (LVEF) There were significant and equivalent reductions in BP SVI LVEDVI and CI 15 minutes after TNG 1 hour after SL ISD and 4 hours after oral ISD in addition to comparative increases in HR and EF by all drugs at these same time intervals The effects of TNG were gone at 30 minutes while changes in LVEDVI LVEF and CI were present 4 hours after SL ISD and persistent changes in LVEDVI and SVI present 6 hours after oral ISD We conclude that nitrates have significant effects on both preload and afterload and that the duration of effects of sublingual and oral ISD are truly long acting as compared to TNG

REFERENCES

1 Battock D J Alvarez H and Chidsey C A E[illegible] propranolol and isosorbide dinitrate on exercise [illegible] ance and adrenergic activity in patients with [illegible] pectoris Circulation 39 157 1969
2 Goldstein R L Rosing D R Redwood D R [illegible] Clinical and circulatory effects of isosorbide di[illegible] Comparison with nitroglycerin Circulation 4[illegible] 1971
3 Battock D J and Chidsey C A Isosorbide di[illegible] angina Circulation 44 1147 1971
4 Battock D J and Chidsey C A Beta adre[illegible] blockade and combination therapy in coronary disease *In* Vogel J H K editor Advances in ca[illegible] ogy Basel Munchen Paris New York 19[illegible] Press Inc Vol 5 p 126 131
5 Aronow W S and Kaplan M A Prop[illegible] combined with isosorbide dinitrate versus pla[illegible] angina pectoris N Engl J Med 280 84[illegible] 19[illegible]
6 Goldbarg A N Moran J F Butterfield T [illegible] Therapy of angina pectoris with propranolol and [illegible] acting nitrates Circulation 40 847 1969
7 Sweatman T Strauss G Selzer A et al The [illegible] acting hemodynamic effects of isosorbide di[illegible] J Cardiol 29 475 1972
8 Klaus A P Zaret B L Pitt B et al Co[illegible] evaluation of sublingual long acting nitrates Cir[illegible] 48 519 1973
9 Goldstein R E and Epstein S E Nitrates in [illegible] prophylactic treatment of angina pectoris Circula[illegible] 48 917 1973
10 Gold H K Leinbach R C and Sanders C A [illegible] sublingual nitroglycerin in congestive heart [illegible] following acute myocardial infarction Circu[illegible] 46 839 1972
11 Franciosa J A Mikulic E Fabie A et al Hemo[illegible] namic effects of oral isosorbide dinitrate in he[illegible] (abst) J Clin Invest 53 25a 1974
12 Gray R Chatterjee K Vyden J et al Isoso[illegible] dinitrate in chronic heart failure (abst) Circu[illegible] 50(Suppl III) 229 1974
13 Levitt P Steele P Vogel R et al Effects of isoso[illegible] bide dinitrate on central circulatory dynamics in cardi[illegible] myopathy (abst) Clin Res 23 396A 1974
14 Steele P Van Dyke D Trow R S et al Simple and safe bedside method for serial measurement of le[illegible] ventricular ejection fraction cardiac output and pulmo[illegible] nary blood volume Br Heart J 36 1[illegible] 1974
15 Najmi M Griggs D M Kasparian H et al Effects of nitroglycerin on hemodynamics during rest and exercise in patients with coronary insufficiency Circulation 35 46 1967
16 Frick M H Balcon R Cross D et al Hemodynamic effect of nitroglycerin in patients with angina pectoris studied by atrial pacing method Circulation 37 [illegible] 1968
17 Parker J O DiGiorgi S and West R O Hemody[illegible] namic study of acute coronary insufficiency precipitated by exercise with observation on the effects of n[illegible] cerin Am J Cardiol 17 470 1966
18 Kasparian H Weiner L Duca P R et al Compara tive hemodynamic effects of placebo and oral isosorbide dinitrate in patients with significant coronary artery disease Am Heart J 90 68 1975
19 William J F Jr Glick G and Braunwald E Studies on cardiac dimensions in intact and unanesthetized man V Effects of nitroglycerin Circulation 32 6[illegible] 1965

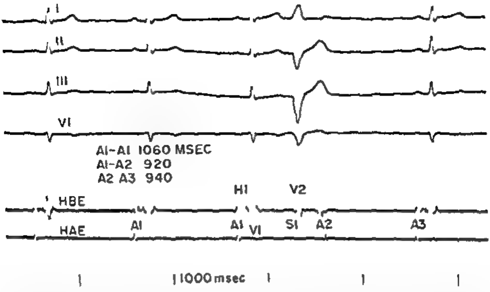

Fig 2 Shortening of the sinus return cycle (*A2 A3*) following a premature ventricular beat in case 11 The sinus cycle l ngth (*A1 A1*) is 1 060 msec A premature ventricular contraction with retrograde atrial depolarization *A2* is associated with sinus node reset and a return cycle length (*A2 A3*) of 940 msec an interval less than the sinus cycle length *S1* = premature ventricular stimulus

e I Onset of sinus node reset with premature atrial and ventricular stimulation*

Case No	*Sinus cycle length (msec)*	*Sinus node reset with atrial stimulation (A1 A2) (msec)*	*Sinus node reset with ventricular stimulation (A1 A?) (msec)*
1	580	510	No reset observed minimum A1 A2 ,60
2	700	460	No reset observed minimum A1 A2 620
3	1 070	800	No reset observed minimum A1 A2 920
4	1 060	780	No reset observed minimum A1 A2 960
5	982	60	,60
6	930	,60	760
7	830	6 0	6 0
[illegible]	1,200	1,040	1 040
9	1 136	1 030	1 0 5
10	987	8.0	800
11	1,220	9.0	960
Mean ± S E M.	968 ± 63	,89 ± 64	

*A1 trial d pol rizat during sinus h thm A2 atrial d polarization p od ed by premature atri l p em ture ntricular stimul t n.

mpulse from the sinus node to the atrium The eturn cycle length (A2 A3) therefore includes he sum of sinoatrial conduction time and A1 A1 f these assumptions are correct the sinoatrial conduction time should equal A2 A3 minus A1 A1 In this and other reports this value has been divided by two since A2 A3 minus A1 A1 theoretically includes conduction into and out of the sinus node In this study antegrade (atrial stimulation) and retrograde (ventriculoatrial conduction) sinoatrial conduction times were calculated from equal A1 A2 intervals during the zone of sinus node reset as half the mean A2 A3 minus the mean A1 A1

Results

Premature atrial and ventricular stimulation were accomplished in all patients without difficulty The results are shown in Tables I and II and Figs 1 and 2

The mean sinus rate was 968 ± 63 msec During premature atrial stimulation a zone of sinus node reset was observed in every patient with the onset at a mean A1 A2 interval of

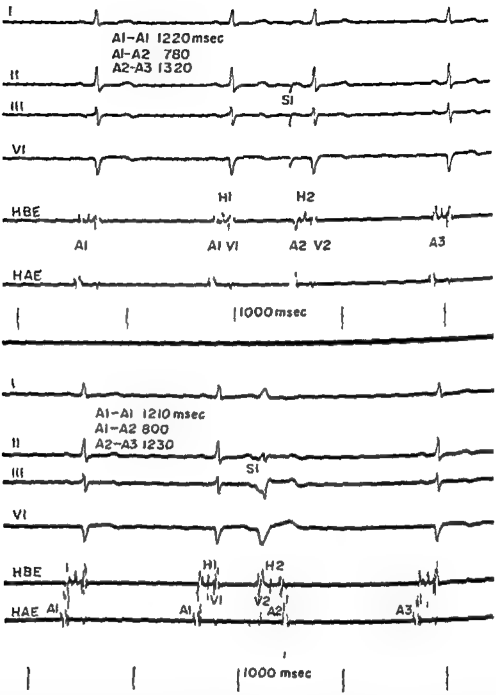

Fig 1 *Comparison of the effect of premature atrial and ventricular stimuli on sinus node function Top panel During a sinus cycle length (A1 A1) of 1 220 msec a premature atrial contraction (A2) with an A1 A2 interval of 780 msec produces sinus node reset with a return cycle length (A2 A3) of 1 320 msec Bottom panel With a similar sinus cycle length a premature ventricular contraction (V2) is associated with retrograde atrial depolarization (A2) with an A1 A2 interval of 800 msec Note that sinus node reset occurs with a return cycle (A2 A3) of 1 230 msec a value less than the return cycle with an equivalent A1 A2 interval during premature atrial stimulation (top panel) S1 = premature ventricular stimulus*

length (A1 A1) and the longest A1 A2 interval producing sinus node reset during premature atrial stimulation were recorded During premature ventricular stimulation the retrograde atrial depolarization (A2) was used to determine the critical A1 A2 interval, and the presence or absence of sinus node reset was recorded The A2 A3 interval during sinus reset was recorded for both atrial and ventricular stimulation

Sinoatrial conduction time was determined by methods previously reported [6] This measurement is based on the assumption that a PAC (A2) which depolarizes the sinus node produces sinus node reset and the return cycle (A2 A3 interval) represents the time necessary to conduct the impulse from the PAC into the sinus node plus the interval until the next sinus depolarization occurs (A1 A1) plus the time to conduct the

cycle length (A2 A3) with ventricular ation was consistently shorter than with If the sinoatrial conduction SACT) is estimated on this basis ventricu l conduction will have a smaller value for There is, however experimental evidence suggests that these measurements may not the true SACT

ultaneous measurements of sinus node and depolarizations in the rabbit heart have d some of the factors which may be respon or the results observed in this study These s have shown that significant discrepancies xist between events in the sinus node and n[10] Retrograde sinus node activation ventricular stimulation may proceed gh different pathways or at a different rate retrograde atrial activation In addition ature impulses which do not penetrate the node may nevertheless affect sinus node ion producing a shortening of the return cycle length It is possible that varying ls of conduction of the impulse from atrial or ncular sites may produce quantitatively rent effects on sinus node function depend n whether the sinus node is penetrated and ict reset or simply effected by interaction adjacent cells Alteration of sinus node tion produced by impulses which do not trate the node would result in obvious errors the estimates of sinoatrial conduction time h relatively crude methods employed in this ly it appears unlikely that the results ined for SACT during ventricular stimula actually represent the correct value The nges in the return cycle length during sinus t with ventriculoatrial conduction appear to shorter than those observed during atrial ulation the mechanism cannot be deter ned from the information available

n case eleven the return cycle was found to be rter than the sinus cycle length Similar inges have been observed in experimental as ll as clinical studies The mechanism is known but a similar effect has been observed to ur in different areas of the sinus cycle with olongation of the return cycle induced by later AC The shortened return cycle in experi ental preparations has been thought to be due low amplitude sinus node depolarizations with short action potential duration perhaps due to a shift in the site of sinus nodal pacemaker activity[11] The additional possibility of sinus node re entry cannot be excluded by present methods

The limitations of surface recordings in the timing of sinus nodal and atrial events permit only a description of the effects of premature ventricular stimulation on sinus node function The results of this study indicate that the retro grade A1 A2 interval associated with alteration of the sinus return cycle may be slightly greater than or equal to the A1 A2 intervals producing sinus reset with premature atrial stimulation No evidence of retrograde atriosinus block was found When the return sinus cycle was effected by ventriculoatrial conduction the A2 A3 interval was consistently less than that produced by atrial stimulation These observations may aid under standing of the electrophysiologic events pro duced by premature ventricular contractions in man

Summary

Although sinus node function has been evalu ated during premature atrial stimulation no study of *retrograde ventriculoatrial sinus node* activation following premature ventricular stim uli has been reported The purpose of this study was to investigate the production of compensa tory and noncompensatory pauses by premature ventricular contractions through a comparison of the effects of atrial and ventricular stimulation on sinus node function

Eleven patients in sinus rhythm were studied with programmed introduction of premature atrial and ventricular stimuli outside the ventric ular vulnerable period The onset of sinus node reset duration of return sinus cycle (A2 A3) during reset and estimated sinoatrial conduction times were recorded Sinus node function during premature ventricular stimulation was approxi mated by utilizing the interval between the last sinus beat and onset of retrograde atrial depolar ization (A1 A2 interval)

The return cycle length (A2 A3) during sinus *reset compared* at equal A1 A2 intervals was significantly less with ventriculoatrial conduction (1145 ± 52 msec atrial vs 1076 ± 52 msec ventriculoatrial $P < 0.01$ by paired t test) and the estimated sinoatrial conduction time was significantly less with ventriculoatrial conduction (71 ± 7 msec atrial vs 25 ± 7 msec ventriculo

Table II Comparison of return cycle length during sinus node reset and estimated sinoatrial conduction time*

Case No	Atrial stimulation: Mean A1 A1	Mean A2 A3	SACT	Ventricular stimulation: Mean A1 A1	Mean A2 A3	SACT
5	982	1 118	68	997	1 050	27
6	930	1 068	69	914	1 018	[illegible]
7	830	980	75	830	890	[illegible]
8	1,200	1 300	50	1 200	1 220	[illegible]
9	1 136	1 235	49	1 130	1 160	15
10	987	1 174	93	1 087	1 120	17
Mean ± S E M	1 010 ± 61	1 145 ± 52	71 ± 7	1 026 ± [illegible]	1 076 ± 52	25 7
p†				NS	*P < 0 01	P < 0 01

A1 A1 interval between sinus beats A2 A3 return sinus cycle after premature atrial beat A2.
†P probability calculated from Student s t test for paired data

789 ± 64 msec During premature ventricular stimulation retrograde atrial depolarization occurred in every case, permitting an estimation of the effect of retrograde atrial stimulation on sinus node function Retrograde sinus node reset was not observed in four patients (cases 1 through 4 in Table I) In these cases the minimum A1 A2 interval produced by retrograde atrial conduction exceeded the minimum A1 A2 interval for sinus node reset observed during antegrade atrial stimulation, and the post PVC pause remained fully compensatory Although ventriculoatrial conduction was intact sinus node reset did not occur because the minimum A1 A2 interval did not fall in the reset zone defined during premature atrial stimulation

Evidence of sinus node reset during ventricular stimulation was obtained in seven patients (cases 5 through 11 in Table I) The retrograde A1 A2 interval at the onset of sinus node reset was equal to the antegrade reset zone in four instances (cases 5 through 8) and exceeded the antegrade zone in three patients (cases 9 through 11) with reset beginning later in the sinus cycle (longer A1 A2 intervals) with retrograde ventriculoatrial conduction In case 11 the return cycle (A2 A3) was altered later in the sinus cycle with retrograde stimulation (Table I) but the return cycle was less than the sinus cycle length (Fig 2 mean A2 A3 950 msec) with ventriculoatrial conduction and greater than the sinus cycle length (mean A2 A3 1 300) during reset with premature atrial stimulation

The return cycles (A2 A3) and estimates of sinoatrial conduction time with atrial and ventricular stimulation were compared in six cases (Table II and Fig 1) Even with the small number of patients studied the values ob for the return cycle length during conduction (1,076 ± 52 msec) were significan less than the A2 A3 intervals with atrial stimula tion (1,145 ± 52 msec , P < 0 01 by paired t te The results of estimated sinoatrial conduction time were also significantly reduced with ventr uloatrial conduction (71 ± 7 msec atrial 25 ± 7 msec ventriculoatrial, P < 0 01 by paire t test) For reasons to be discussed this value ma not accurately represent retrograde sinoatri conduction time, but may reflect a differen sequence or rate of sinus node activation

Discussion

This study illustrates some features of the interaction of premature ventricular contractions and ventriculoatrial conduction with the sinus node Although premature ventricular beats m exhibit retrograde conduction to the atria if the retrograde impulse does not fall within a critical area (zone of reset) the normal sinus cycle will not be interrupted and a compensatory pause will occur (cases 1 through 4 and Table I) The retrograde zone of sinus node reset following a premature ventricular beat appears to correspond to the zone of reset with premature atrial stimulation although slight differences may exist In three patients (cases [illegible] through 11) the onset of alterations in the sinus return cycle occurred at slightly longer A1 A2 intervals with premature ventricular stimulation than premature atrial depolarization In addition, the alteration in

…ilarity of renal glomerular hemodynamics in mammals

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…ite the approximately 70 million-fold varia… in body weight of mammals (shrew to whale) …heart lungs kidneys and other major organs … much similarity in morphology and func… Evidence has been presented that over the …st range of mammals quantitative morpho…al and functional characteristics of these and …r organs are described by power law equa…s relating the particular variable to body …ght. Stahl has shown by applica… of engineering dimensional analysis to physi… utilizing the cancellation of statistically …ed power law prediction formulas for various …siological parameters that it is possible to …ain dimensionless constants and dimensionless …sign criteria which characterize integrated …mmalian physiological functions

The glomerular circulation has been described … a system of capillaries in parallel circuits …ving cross connections By applying Poi…uille s law to the flow of blood through these …merular capillary circuits and utilizing power … equations describing the relationship between …dy weight and glomerular number glomerular …lume renal blood flow and glomerular filtra…on rate it has been possible to calculate the …umber and length of capillaries in the mammali… glomerulus Evidence will be presented to …ow that the average length of the glomerular …pillaries average linear velocity of blood flow …erage time that blood spends in the capillaries blood flow per unit time per unit glomerular capillary surface area and the glomerular filtration rate per unit time per unit surface area are all constant regardless of the size of the mammal

Methods

Microscopic measurements of glomerular diameter and volume were made in plastic corrosion casts of three rats two rabbits four dogs one goat one horse and one cow Casts were prepared of the entire arterial system as follows after anesthesia and cannulation of the carotid and femoral arteries the animals were killed by injecting concentrated KCl into the arch of the aorta and immediately bled Batson s Compound* was then injected under 100 mm Hg pressure into the carotid and femoral arteries and the pressure maintained until the plastic hardened This took between 30 and 60 minutes in different experiments Following this the animal was macerated in concentrated potassium hydroxide solution (15 to 33 per cent) and the remaining arterial cast washed with water until it was free of all remaining tissue

The kidneys of these casts were removed and the diameters of 50 or more of the glomerular capillary tufts measured with a binocular microscope and the average diameter determined Glomerular volume V was calculated by the equation

$$V = 4/3 \pi (D/2)^3$$

where D is diameter of the glomerulus

Data in different mammalian species were collected from the literature for glomerular volume number of glomeruli effective renal plasma flow measured either with Diodrast or para amino hippurate and for glomerular filtration

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atrial, $P < 0.01$ by paired t test) Ventriculoatrial sinus reset occurred later in the sinus cycle than atrial reset in three of seven patients with sinus reset produced by both atrial and ventricular prematures

This study shows that the effects of ventriculoatrial conduction on sinus node function are significantly different from those of atrial stimulation alone The return sinus cycle length during reset and estimated sinoatrial conduction time are significantly reduced with ventriculoatrial conduction Although the zones of sinus reset with atrial and ventricular stimulation are approximately equal, ventriculoatrial depolarization may produce sinus reset later in the sinus cycle in some cases

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REFERENCES

1 Bussan [illegible] Torin S and Scherf D Retrograde conduction of ventricular extrasystoles to the atria Am J Med Sci 230 293 19[illegible]

2 Goldreyer B N and Bigger J T Jr Ventriculoatrial conduction in man Circulation 41 935 1970

3 Wit A L Weiss M [illegible] Berkowitz W D Rosen K M Steiner C and Damato A N Patterns of atrioventricular conduction in the human heart Circ Res 27 345 1970

4 Bissett J K de Soyza N Kane J J and [illegible] N M Improved sinus node sensing after a [illegible] Heart J in press.

5 Strauss, H C Saroff A L Bigger J T [illegible] Giardina E C Premature atrial stim[illegible] the understanding of sinoatrial co[illegible] Circulation 47 86 1973

6 Reiffel J A, Bigger J T Jr and Konstam, [illegible] relationship between sinoatrial conduction [illegible] sinus cycle length during spontaneous sinus [illegible] in adults Circulation 50 9[illegible] 19[illegible]

7 Goldreyer [illegible] N, and Damato A N [illegible] entrance block Circulation 44 [illegible]89 19[illegible]

8 Paulay K L Varghese J P and Damato, [illegible] rhythms in response to an early atrial prema[illegible] larization in man Am Heart J [illegible] [illegible]

9 Bigger J T Jr and Strauss, H C The [illegible] sinoatrial node function in man [illegible]

10 Miller H C and Strauss, H C Measur[illegible] sinoatrial conduction time by premature atrial s[illegible]tion in the rabbit Circ Res 35 935 19[illegible]

11 Klein H O Singer D H and Hoffman B F E[illegible] atrial premature systoles on sinus rhythm in the [illegible] Circ Res 32 480 1973

12 Fleischmann P Interpolation of atrial premature [illegible] of intra atrial origin due to concealed A-S cond[illegible] Am Heart J 66 309 1963

13 Katz L N and Pick A Clinical electrocardio[illegible] Arrhythmias, Philadelphia 19[illegible]6 Lea & Febiger [illegible]ers.

14 Langendorf R Lesser M E Plotkin P and [illegible] B D Atrial parasystole with interpolation [illegible]tions on prolonged sinoatrial conduction Am Hear[illegible] 63 649 1962

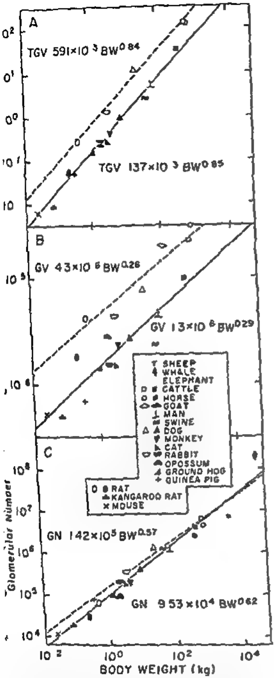

Fig 1 Logarithmic relationships between body weight and total glomerular volume in one kidney, number of glomeruli in one kidney, and average single glomerular volume in 18 species of mammals (mouse to whale). The closed symbols and solid lines represent data taken from the literature. The open symbols and broken lines represent data obtained by means of air plastic injection casts. Equations for the solid lines are given below the lines; equations for the broken lines are given above the lines. Total glomerular volume and individual glomerular volume are in milliliters; body weight is in kilograms.

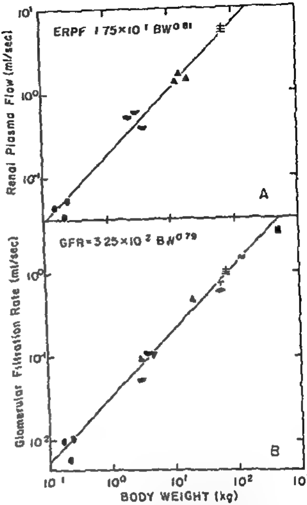

Fig 2 Logarithmic relationships between body weight and effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) in 10 species of mammals (rat to bovine). The data were taken from the literature in which effective renal plasma flow was measured by means of either diodrast or para amino hippurate and glomerular filtration rate was measured by means of inulin. Body weight is in kilograms.

uli (GN) and body weight for these mammals* is shown in Fig 1 C. This relationship is described by the equation

$$GN = 1.42 \times 10^{5}\ BW^{0.57} \quad (3)$$

where BW is in kilograms. Also Fig 1 C shows the same relationship for mammals varying 1.5 million-fold in body weight (mouse to whale) utilizing values reported in the literature. This relationship is described by the equation

$$GN = 9.53 \times 10^{4}\ BW^{0.62} \quad (4)$$

Total glomerular volume The average glomer

*Excluding the goat

Table I Power law parameters for glomerular volume, number, filtration rate effective renal pla… flow, and body weight for a wide variety of mammals (mouse to whale)

Variables (units)	Species	Power law coefficients					
		a	b	r	N	s_a	S_E
Glomerular capillary tuft volume (ml)	Rat rabbit goat dog horse cow	4 30 × 10 ⁴	0 26	0 94	6	2?6	4…
Glomerular volume (ml)	Mouse kangaroo rat rat guinea pig ground hog opossum rabbit cat monkey dog man swine cattle elephant	1 30 × 10	0.29	0.94	14	23.4	36…
Glomerular number	Rat rabbit dog horse cattle	1 42 × 10	0 57	0 99	5	86.9	3 1…
Glomerular number	Mouse kangaroo rat rat guinea pig ground hog opossum rabbit cat monkey dog man horse cattle swine elephant whale	9 53 × 10	0 62	0 98	16	?9 3	43.3…
Total glomerular volume (ml)	Rat rabbit dog horse cattle	5 91 × 10 ⁴	0 84	0 99	5	61 8	2 3…
Total glomerular volume (ml)	Mouse kangaroo rat rat guinea pig ground hog opossum rabbit cat monkey dog swine man cattle elephant	1 37 × 10	0 85	0 99	14	16 4	?6.0…
ERPF (ml sec)	Rat rabbit dog man	1 75 × 10	0 81	0 99	1?	?0 1	?3.1…
GFR (ml sec)	Rat rabbit cat dog man monkey goat sheep swine cattle	3 25 × 10 ²	0 79	0 99	15	17 1	?2.2…

Statistical fit is to the equation y = a BW Body weight is in kilograms r correlation coefficient N total number of data points s_a 95 per… confidence limits of a in per cent S_E mean (±) standard error of the estimate in per cent s_b [illegible] per cent confidence limits of b in slope …

rate measured with inulin [6,8,9,11,1,17,21,5,29,31,32] The average value of these parameters for an animal of average weight for each species was calculated and employed in the analysis below Log log plots were prepared of the relationship between body weight and glomerular number glomerular volume total glomerular volume effective renal plasma flow and glomerular filtration rate in one kidney The data were transformed to base 10 logarithms and the linear regression of the logarithmic values calculated by the method of least squares to give the parameters in the power law formula

$$y = aX^b$$

where y is any variable and X is mass of body weight in kilograms Statistical analysis of the logarithmic equations included the correlation coefficient (r) 95 per cent confidence limits for repeated line fits (s_a and s_b) and the standard error of the estimate, S_E which has much the same significance for a logarithmic regression line as the standard deviation for a mean, i e , two S_E limits should include 95 per cent of the cases With log log analysis, $+S_E$ and $-S_E$ differ slightly the values shown in the table are the mean of the two values

Results

Table I presents the coefficients for the pow… law regression equations, as well as the stati… measures for the relationship of these variable… body weight

Glomerular capillary tuft volume and bod… **weight** The logarithmic relationship between th… experimentally determined glomerular capilla… tuft volume and body weight in mammal… extending over a 1 740 fold range (rat to horse) body weight is shown in Fig 1, *B* and described b… the equation

$$GTV = 4\,30 \times 10^{4}\, BW^{0\,26} \quad (1$$

where GTV is glomerular tuft volume in mill… liters and BW is body weight in kilograms Al… Fig 1 *B* shows the relationship for glomerul… volume and body weight in mammals ranging ?… thousand-fold in body weight (mouse to ele… phant), utilizing values reported in the literatu… This relationship is described by the equation

$$GV = 1\,30 \times 10\,{}^{*}BW^{0\,29} \quad ($$

Glomerular number and body weight The number of glomeruli in one kidney for the sam… species of animals shown in Fig 1 *B* was dete… mined from studies in the literature The logarith… mic relationship between the number of glome…

g r to have a value of 4×10^{-4} cm the ion becomes

$$TGV = N\ L\ (5.02 \times 10^{-7}) \quad (12)$$

otal glomerular volume for the animals that tudied having distended glomeruli and bed by Eq (5) is the same as that given in 12) equating the two and solving for N

$$N = \frac{117.7 \times 10\ BW}{L} \quad (13)$$

both this equation and Eq (11) give the number of glomerular capillaries in one y they must be equal to each other ting the two and solving for L gives

$$L_c = 7.33 \times 10\ \ BW \quad (14)$$

e L_c is in centimeters and BW is in kilograms BW[0.15] is so near to BW and is within the er cent confidence limits of the power func from which it was derived it appears onable to assume that its value is BW which a value of 1 Thus the length of the average llary is constant regardless of the size of the amal and has a value of 733 microns

ubstituting in Eq (13) this value for L gives equation for the total number of glomerular llaries in one kidney i e

$$N = 16.1 \times 10^{6}\ BW \quad (15)$$

elocity of flow in glomerular capillaries al capillary cross section in all glomeruli in kidney is equal to the number of capillaries in parallel circuits of all glomeruli times the ss section of an individual capillary i e

$$XS = N\ \pi(r)$$

ere N is the number of capillaries and r is the rage capillary radius Substituting the number distended capillaries given in Eq (15) and ing the radius of the average capillary to be 4 crons gives

$$XS = 809 \times 10\ \ BW \quad (16)$$

ere XS is the total capillary cross section in all omeruli in one kidney in square centimeters d BW is in kilograms

Linear velocity is equal to volumetric flow rate ided by cross section Thus dividing Eq (8) for e flow through all the glomeruli in one kidney y Eq (16) for the cross section gives the average near velocity in the average capillary

$$V = 0.039\ BW \quad (17)$$

here V is in cm sec and BW is in kilograms ince BW in the equation is small and is ithin the variation of the 95 per cent confidence limits of the power functions from which it was derived it is assumed to be BW[0] and the equation becomes

$$V = 0.039\ cm\ \ sec^{-1} \quad (18)$$

Thus, the average velocity through the average capillary is constant regardless of the size of the mammal

Time spent in glomerular capillaries The time spent in traversing the length of a capillary is equal to the length divided by the velocity Since the average velocity through the glomerular capillaries as shown above is 0.039 cm sec and the average capillary length is 7.33×10^{-2} cm the average time blood spends in the capillaries is

$$T = 1.88\ sec \quad (19)$$

Thus this time is constant regardless of the size of the mammal

Blood flow per unit capillary surface area in the mammalian glomerulus Assuming that the glomerular capillary tuft is made up entirely of capillaries the total capillary surface area in one kidney is equal to the product of the length and circumference of the average capillary multiplied by the number of capillaries i e

$$SA = L\ N\ 2\pi r_c$$

Substituting Eq (14) for the length of the average capillary and Eq (15) for the number of capillaries and taking capillary radius to be 4 microns gives

$$SA = 2966\ BW \quad (20)$$

where the surface area is in square centimeters and BW is in kilograms The blood flow through all glomeruli in one kidney regardless of the size of the mammal is given by Eq (8) Dividing this equation by Eq (20) for the surface area of the capillaries in all glomeruli in one kidney gives

$$FGB/SA = 1.07 \times 10^{-4}\ BW^{0.0} \quad (21)$$

where FGB/SA is blood flow per unit capillary surface area in ml sec cm^{-2} and BW is in kilograms Since BW is small and is within the variation of the 95 per cent confidence limits of the power functions from which it was derived it is assumed to be BW and the equation becomes

$$FGB/SA = 1.07 \times 10\ \ ml\ \ sec^{-1}\ \ cm^{-2} \quad (22)$$

Thus the amount of blood flowing per unit surface area of glomerular capillary per unit time is constant regardless of the size of the mammal

Glomerular filtration rate and body weight

ular volume and body weight were calculated for each species in which we prepared plastic glomerular tuft casts. With the data from the literature the number of glomeruli was calculated for these animals. The product of glomerular volume and glomerular number for each species was calculated, giving the total glomerular volume in one kidney for an animal having a body weight equal to the average body weight of the animals studied. The logarithmic relationship between total glomerular volume and body weight for these animals varying 1,740 fold in body weight is shown in Fig. 1 A and is described by the equation

$$\mathrm{TGV} = 5.91 \times 10^{[illegible]}\,\mathrm{BW}^{0.[illegible]} \qquad (5)$$

where TGV is in milliliters and BW is in kilograms. In a similar manner utilizing values from the literature total glomerular volume was calculated for mammals ranging 216 thousand-fold in body weight (mouse to elephant). The logarithmic relationship between total glomerular volume and body weight for these animals is shown in Fig. 1 A and is described by the equation

$$\mathrm{TGV} = 1.37 \times 10^{[illegible]}\,\mathrm{BW} \qquad (6)$$

Effective renal plasma flow and body weight The logarithmic relationship between body weight and effective renal plasma flow through one kidney measured by para amino hippurate or Diodrast clearance techniques in studies reported in the literature for mammals varying 446 fold (rat to man) in body weight is shown in Fig. 2 A and described by the equation

$$\mathrm{ERPF} = 1.75 \times 10^{[illegible]}\,\mathrm{BW}^{[illegible]} \qquad (7)$$

where ERPF is effective renal plasma flow in ml sec^{-1} and BW is in kilograms. Assuming an hematocrit of 0.45, this can be corrected to blood flow through one kidney to give

$$\mathrm{ERBF} = 3.18 \times 10^{[illegible]}\,\mathrm{BW}^{[illegible]} \qquad (8)$$

Average glomerular capillary length and number The volume of the glomerular capillary tuft in our plastic injection casts consists of the injected capillaries, intraglomerular parts of the afferent and efferent arterioles, plus space between the capillaries. Although it is not known what fraction of the injected capillary tuft consists of space between capillaries, separation of the capillaries by breaking the cast into small pieces showed that the capillaries were closely packed together and that there was minimal space between them. Likewise it is not known what fraction of the injected capillary tuft consists of afferent and efferent vessels [illegible] presumably this volume is a small fraction of [illegible] total. Thus, in the analysis given below for [illegible] and number of capillaries in the glomeruli [illegible] have assumed that in the plastic glomeruli [illegible] the volume measured is 100 per cent capillaries [illegible] parallel circuits.

Since the blood flow through all of the glomeruli in one kidney from the downstream end of the afferent arteriole to the upstream end of the efferent arteriole is through a system of capillaries in parallel, the total flow is described [illegible] first approximation by Poiseuille's law [illegible] follows

$$\mathrm{FGB} = \frac{N_c\,\Delta P\,\pi\,(r_c)^4}{8\,L_c\,\eta} \qquad (9)$$

where FGB is the blood flow through all glomeruli in one kidney in ml sec^{-1}, N_c is the number of capillaries in all of these glomeruli, r_c is [illegible] average capillary radius, L_c is the average capillary length, ΔP is the average pressure drop [illegible] the beginning to the end of the capillary and [illegible] the coefficient of viscosity of blood.

It is generally agreed that the coefficient of viscosity of blood, the diameter of the capillaries and arterial capillary, and venous pressures [illegible] not differ significantly in mammals of different size. In contrast the exact value of the pressure drop from beginning to end of the glomerular capillaries is not known. However recent measurements of this pressure drop in the rat and monkey have shown that it is small being [illegible] greater than 2.5 mm Hg.[3, 4, 7] Substituting in Eq (9) this value for ΔP as a first approximation the mean value for blood viscosity of [illegible] dynes sec cm^{-2} and capillary diameter of [illegible] gives

$$\mathrm{FGB} = \frac{1.46 \times 10^{[illegible]}\,N}{L_c} \qquad (10)$$

where the flow is in ml sec^{-1}. Since this flow [illegible] the same as that given in Eq (8) equating the two and solving for N gives

$$N = 2.18 \times 10^{[illegible]}\,\mathrm{BW}^{0.[illegible]}\,L \qquad (11)$$

where BW is in kilograms.

Assuming that the volume of the glomerular capillary tuft measured in our plastic injection specimens consists of 100 per cent capillaries [illegible] total glomerular tuft volume in one kidney equals the number of capillaries in all of the glomeruli times the volume of the average capillary, i.e.

$$\mathrm{TGV} = N_c\,(\pi r_c^2\,L_c)$$

— cent of our measured volume It will be noted —he table that the deviation from the values —ployed in our calculations, was less than 50 per t in all cases except two (capillary number and ss section) in which the deviation was 100 per t when the pressure drop was taken to be 0 625 . Hg This difference is small when considered elationship to the over all pattern of function ich extends more than 446 fold in body weight s interesting to note in Table II that the time t blood spends in glomerular capillaries is ependent of pressure drop blood viscosity and ius This suggests that if in a particular cies or animal one or more of these factors iate from the values that we have employed in calculations, then this animal or species has appropriate change in capillary length and mber such that the blood transit time through glomerular capillaries is constant Until such ne as more information is available on the essure drop in large and small mammals we nnot be certain that the pressure drop is the me regardless of mammal size If the pressure op differs from animal to animal or species to ecies however it is to be emphasized that gardless of this the time that blood spends in e capillaries remains constant (Table II)

In view of the fact that regardless of mammal ze, the factors involved in the formation of the otein free glomerular filtrate are approximate the same i e (1) hydrostatic pressure in the ipillary forcing filtrate through the capillary all (2) colloidal osmotic pressure of the blood roteins (3) hydrostatic pressure in the collecting ubules of the kidney and as shown above (4) lood flow per unit glomerular capillary surface rea per unit time it would appear that the number and average length of capillaries in the lomerulus are related in such a manner that lood spends a constant time in the capillaries in rder that the glomerular filtration rate per unit surface area of capillaries is constant regardless of nammal size The large amount of glomerular filtrate formed in the large mammal comes about as a result of the greater total glomerular surface area

The volumes of the distended glomerular capillary tufts that we measured were considerably larger than the glomeruli of the same species reported by other investigators [? ? ??] in which the glomeruli were not distended and an unknown amount of shrinkage had taken place during histological preparation It might be argued that our distended glomerular capillaries were larger than during life and that as a result the calculated values for the hemodynamic variables were in error Comparisons of our values for the above variables with the values obtained when calculated from data on undistended glomeruli described in the literature assuming as did Vimtrup[?] that the glomerulus consists of 50 per cent capillaries are given in Table II As shown in the table the values of the various parameters for undistended glomeruli differ considerably from our values The hydrostatic pressure in the glomerular capillaries has been reported to be 45 mm Hg and it would appear that the volumes of the glomerular tufts in our plastic casts, in which a high injection pressure was maintained until the plastic hardened were closer to the volumes existing during life than would be the volume with no distending hydrostatic pressure in the capillaries.

When information becomes available on a wider range of mammals particular values given for the pattern of function that we have described will no doubt be changed to some extent We believe however that these differences will be small and will not alter the description of the general similarity pattern of function as presented

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REFERENCES

1. Adolph, E A Quantitative relations in the physiological constitutions of mammals, Science 109 579 1949
2. Bolomey A A. Michie A. J., Michie C., Breed F S., Schreiner G E and Lauson H D Simultaneous measurement of effective renal blood flow and cardiac output in resting normal subjects and patients with essential hypertension J Clin. Invest. 28 10 1949
3. Brenner B M., Troy J L. and Daugharty T M The dynamics of glomerular ultrafiltration in the rat J Clin In est. 50 1776 1971
4. Brenner B M., Troy J L. Daugharty T M Deen W M and Robertson C R. Dynamics of glomerular ultrafiltration in the rat II Plasma flow dependence of GFR, Am. J Physiol. 223 1191 1972
5. Brody S Bioenergetics and growth, New York, 1945 Reinhold Publishing Company
6. Chasis, H Redish, J Goldring W Ranges H A and Smith, H W The use of sodium p-aminohippurate for the functional evaluation of the human kidney J Clin Invest 24 583 1945
7. Deen W M Robertson C R., and Brenner G M Glomerular ultrafiltration Fed. Proc 33 14 1974
8. DeJongh, D K., and Kok K Investigation into the estimation of inulin and PAH clearances in rats, Acta Physiol. Pharmacol. Neerl. 4 222 1955

Table II Renal glomerular hemodynamic constants and variables in mammals*

Hemodynamic parameters	Glomerular capillary tuft: Distended A	Glomerular capillary tuft: Undistended B	Change of value shown in column A (in per cent): ΔP (1 25)	ΔP (0 625)	Viscosity (0 0114)	Radius (5μ)	Hematocrit (0 40)	Column (90%)	C
Glomerular capillary									
Length (cm)	7 33 × 10	2 50 × 10	−29	−50	+42	+25	+5	−5	
Number	16 1 × 10 BW	5 5 × 10 BW	+41	+100	−30	−49	−5	−6	
Cross section (sq cm)	809 × 10 BW	274 × 10 BW	+41	+100	−30	−20	−5	−6	
Velocity (cm sec)	0 039	0 116	−29	−50	+42	+25	−3	+6	
Surface area (sq cm)	2966 BW	312 BW	0	0	0	−20	0	−11	
Time (sec)	1 88	0 22	0	0	0	0	+8	−10	
FGB/SA (ml cm sec)	1 07 × 10	9 30 × 10	0	0	0	+25	−8	+12	
GFR/SA (ml cm sec)	0 11 × 10	0 95 × 10	0	0	0	+25	0	+12	

The constant value regardless of body size of average glomerular capillary length velocity of blood flow time that blood spends in the glo capillaries blood flow per unit capillary surface area (FGB/SA) and glomerular filtration rate per unit capillary surface area (GFR/SA) and the law equations describing the number of capillaries total cross section of capillaries and total surface area of capillaries in all glomeruli in one kidney given The values of the distended capillaries were calculated from our plastic injection casts the values for undistended capillaries were calc the use of data from the literature in which the glomerular capillaries were not distended These values and equations were calculated taking viscosity to be 0 0228 dyne sec cm hematocrit 0 4 capillary radius 4μ, the pressure drop from beginning to end of the capillary to be 2 5 mm and glomerular tuft volume to be 100 per cent of the measured volume The values in the columns under Per cent changes from value in Column A were calculated with the same values employed in the calculations for Column A except that one of the values was changed for calculations in each column as shown i e ΔP of 1 25 and 0 625 instead of 2 5 mm Hg blood viscosity of 0 0114 dynes sec cm instead of capillary radius of μ instead of 4 hematocrit of 0 40 instead of 0 45 and capillary tuft volumes of 90 and 45 per cent of the measured volume instead of 100 per cent

The logarithmic relationship between glomerular filtration rate in one kidney and body weight in mammals ranging 438 fold (rat to man) in body weight is shown in Fig 2, *B* This relationship is described by the equation

$$GFR = 3\ 25 \times 10^{-4}\ BW^{0\ 78} \qquad (23)$$

where GFR is in ml sec ¹ and BW is in kilo grams

Dividing Eq (23) for glomerular filtration rate by Eq (20) for total glomerular capillary surface area gives the glomerular filtration rate per unit surface area of glomerular capillaries *GFR/SA* i e ,

$$GFR/SA = 0\ 11 \times 10 \quad BW \qquad (24)$$

where GFR/SA is in ml cm ² sec ¹ of glomerular capillary surface Since the power function of BW ⁰⁰ is small and within the 95 per cent confidence limits of the power functions from which it was derived it is assumed to be zero Thus the glomerular filtration rate per unit capillary surface area is constant regardless of the size of the mammal and has a value of 1 1 × 10 ⁵ ml cm ² sec ¹

Discussion

It is to be emphasized that the data given here are for normal adult mammals varying greatly in size and extending over many species We belie that the relationships described formulate c similarity criteria which define the normal ad mammalian design of the cardiovascular fu tions studied These relationships differ to s extent from species to species and from animal animal, depending on the degree of adaptation different environmental situations during course of evolutionary development These diffe ences from the normal pattern are limited a define to some degree the deviation from t normal that an animal or species might have a yet still survive

If in a particular species or individual anima it is known that one or more of the hemodynam variables differ from the values used in t calculations employed here, then more accura calculations may be made employing the var bles which differ from the ones we used This particular importance in the case of the pres drop because all that is known is that it is greater than 2 5 mm Hg It may be that it ha value of some fraction of 2 5 mm Hg In Table examples are shown where the pressure drop taken to be 1 25 and 0 625 mm Hg, blood visco 0 0114 poise capillary radius 5 microns hema crit 0 40 and glomerular tuft volumes of 90 and

ECG and VCG changes in experimental hemiblock and bifascicular block

ashi Okuma M D

a Japan

ny studies[1-14] have been done since Rosenbaum[9] presented the concept of hemiblock but there exists a diversity of opinion regarding the changes in the direction of the initial part of the QRS forces and the degree of axis shift in the diagnosis of hemiblock Experimental work on this point has been undertaken by Uhley and Rivkin,[4] Watt and associates[5-10] and Medrano and associates but their approaches involved some unresolved points including (1) inadequacy from the viewpoint of the lead system (2) error due to an unreliable cutting technique and (3) the indispensability of inflicting an injury on the ventricular free wall at the time of cutting

These disadvantages in animal experiments on bundle branch block are of great concern and not to be overlooked Our method which has been previously described[3] was improved with respect to these points. The patterns of QRS configuration obtained by our method were similar to those of human subjects With this method electro and vectorcardiographic changes of QRS configuration were studied before and after left anterior subdivision block (LASB) isolated and combined with right bundle branch block (LASB combined with RBBB) in canine hearts In another series left posterior subdivision block (LPSB) isolated and combined with right bundle branch block (LPSB combined with RBBB) were also studied

Material and method

Adult mongrel dogs weighing 7 to 12 kilograms were anesthetized with sodium pentobarbital (50 mg per kilogram) intraperitoneally Each dog was evaluated as normal by recording the standard 12 lead electrocardiograms (ECG s) in situ and no abnormalities of QRS configuration were found The chest was opened under artificial respiration After excision from the chest the heart was immediately perfused with oxygenated Tyrode s solution held at about 37° C by means of Lagendorff's technique and placed in a cylindrical torso model filled with Tyrode s solution The position of the heart was so selected that ECG s obtained from the torso surface resembled those from the human body Standard 12 lead ECG s and Frank lead vectorcardiograms (VCG s) were recorded before and after cutting the specific site of the left and right bundle branches A brief outline of the experimental apparatus is shown in Fig 1

Fig 2 shows the distribution of the canine intraventricular conduction system Photographs such as this were taken after each experiment to confirm the site of incision In order to make the distribution of Purkinje fibers easy to see the endocardial surfaces of both ventricles were stained with Lugol s solution The upper portion of Fig 2 shows the left septal surface The main left bundle appears beneath the aortic valve and spreads out on the subendocardium like a fan then divides into two subdivisions One subdivision reaches to the anterior papillary muscle and the other runs toward the posterior papillary muscle The intermediate portion of both subdivisions forms the Purkinje network

The lower photograph in Fig 2 shows the right septal surface The main right bundle appears as a bundle beneath the tricuspid valve courses to the anterior papillary muscle without branching and then separates into three subdivisions In order to cut a subdivision of the left bundle and the main right bundle a left or right atriotomy was done and after removal of the mitral valve or

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9 Dicker S E and Heller H The mechanism of water diuresis in normal rats and rabbits as analyzed by inulin and diodone clearances J Physiol 103 449 1945
10 Forster R P An examination of some factors which alter glomerular activity in the rabbit kidney Am J Physiol 150 523 1947
11 Friedman S M Polley J R and Friedman C L The clearance of inulin and sodium p aminohippurate in the rat Am J Physiol 150 340 1947
12 Goldring W Chasis H Ranges H A and Smith H W Relations of effective renal blood flow and glomerular filtration to tubular excretory mass in normal man J Clin Invest 19 739 1940
13 Gunther B On theories of biological similarity in Fortschritte der experimentellen und theoretischen Biophysik Leipzig 1975 Georg Thieme Verlag Band 19
14 Hall [illegible] V Studies of normal glomerular structure by electron microscopy in Proceedings of the Fifth Annual Conference on the Nephrotic Syndrome New York 1953 National Nephrosis Foundation pp 1 39
15 Hall B V Further studies of the normal structure of the renal glomerulus Proceedings of the Sixth Annual Conference on the Nephrotic Syndrome New York 1954 National Nephrosis Foundation pp 1 39
16 Houck C R Statistical analysis of filtration rate and effective renal plasma flow related to weight and surface area in dogs Am J Physiol 153 169 1948
17 Kaplan [illegible] I and Smith H W Excretion of inulin creatinine xylose and urea in the normal rabbit Am J Physiol 113 354 1935
18 Korner P I Renal blood flow glomerular filtration rate renal PAH extraction ratio and the role of the renal vasomotor nerves in the unanesthetized rabbit Circ Res 12 353 1963
19 Kunkel P A The number and size of the glomeruli in the kidney of several mammals Bull Johns Hopkins Hosp 47 285 1930
20 Lippman R W Clearances as a mea[illegible] function in the rat Am J Physiol 152 [illegible] 19[illegible]
21 Moustgaard J Inulin hippodin clearance in [illegible] dogs Skand Veterinar tidskr 35 508 1945
22 Oliver J Nephrons and kidneys, New Yo[illegible] Harper & Row Publishers p 48
23 Rytand D A The number and size of ma[illegible] glomeruli as related to kidney and to body we[illegible] methods for their enumeration and measureme[illegible] J Anat 62 507 1937
24 Smith H W The kidney Structure and func[illegible] health and disease Oxford 1951 Oxford Univer[illegible] Press p 570
25 Smith W W Renal blood flow and mannitol d[illegible] the rabbit Bull Mt Desert Island Biol Lab 43 5 1941
26 Stahl W R Scaling of respiratory varia[illegible] mammals J Appl Physiol [illegible] 453 1961
27 Stahl W R Similarity and dimensional m[illegible] biology Science 137 138 205 1962
28 Stamler J Katz L N and Rodbard S Renal [illegible] clearances in dogs with nephrogenic and [illegible] hypertension J Exp Med 90 511 1949
29 Sweet A Y Levitt M F and Hodes H L [illegible] function body fluid compartments and water and [illegible] trolyte metabolism in the monkey Am J Ph[illegible] 201 975 1961
30 Vimtrup B J On the number shape structure [illegible] surface area of the glomeruli in the kidneys of ma[illegible] mammals Am J Anat 41 123 1928
31 Vogel G Zur Bestimmung von glomerularer F[illegible] tionsrate und filtrierender Flache in der Niere [illegible] Haussaugetiere Pflugers Arch 269 264 1959
32 Wirz H Untersuchungen über die Nierenfunktion be[illegible] adrenalektomierten katzen Helv Physiol Acta 3 [illegible] 1945

Fig. 3 Typical ECG changes with left anterior subdivision block (*LASB*) alone and left anterior subdivision block combined with right bundle branch block (*LASB combined with RBBB*) Left control patterns middle after production of LASB right after production of LASB combined with RBBB

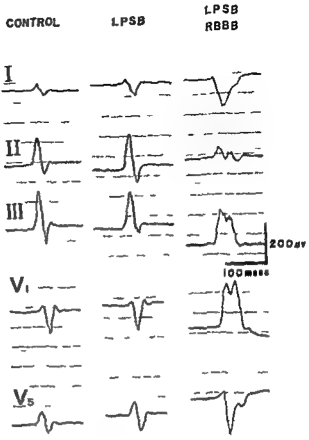


Fig 4 ECG changes with left posterior subdivision block (*LPSB*) alone and left posterior subdivision block combined with right bundle branch block (*LPSB combined with RBBB*)

(LPSB) and left posterior subdivision block combined with right bundle branch block (LPSB combined with RBBB) Fig 4 shows a typical example of LPSB alone and LPSB combined with RBBB With LPSB (middle tracing) the S wave in Lead I increased but the R in Lead III was diminished Â QRS was shifted from +90 to +125° QRS duration was widened only from 56 to 58 msec After LPSB combined with RBBB deep S waves appeared in Leads I and V_5 and a tall R wave in Lead V The QRS duration was prolonged to 82 msec and Â QRS was shifted to +145

VCG patterns

1 Changes in LASB and LASB combined with RBBB Fig 5 shows a typical example of LASB alone and LASB combined with RBBB The subject in this case is not the same dog as the one described in Fig 3 The control tracing (upper) shows, in the frontal plane the QRS loop directed to the left and inferiorly In the left sagittal plane the QRS loop is directed to the front and inferiorly The horizontal plane shows the QRS loop directed to the left The direction of rotation is counterclockwise in all projections With LASB alone the main body and terminal portion were displaced to the front and superiorly but the direction of the initial portion of the efferent limb showed no essential changes The direction of rotation remained unchanged in all projections After LASB combined with RBBB the afferent limb of the QRS loop was displaced more to the front and superiorly and the terminal portion of the QRS loop was inscribed slowly The direction of rotation was changed from counterclockwise to a figure of eight configuration in the horizontal and left sagittal plane

2 Changes in LPSB and LPSB combined with RBBB Fig 6 shows a typical example of LPSB alone and LPSB combined with RBBB This VCG was obtained from the same dog as the ECG in Fig 4 The direction of rotation of the QRS

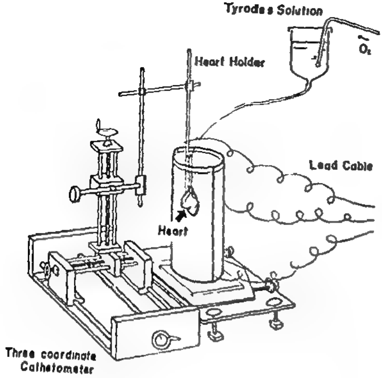


Fig 1 Schematic illustration of the experimental apparatus

tricuspid valve the particular site in the conduction system was cut under direct visualization By this technique since the author could make sure of the site of conduction system to be cut no damage was inflicted on the ventricular free wall except the site of the incision

In addition to the standard 12 lead ECG s Frank lead VCG s were recorded from electrodes fixed on the surface of the torso model The positions of the electrodes were selected conventionally to correspond with those of human beings

The polarities of the Frank lead system were designated as follows Lead X (polarity positive to the right as viewed from the front) Lead Y (polarity positive to downward direction) and Lead Z (polarity positive anteriorly) respectively ECG's and VCG s were amplified with a main amplifier (Yokokawa electric TYPE 3122) via a preamplifier (Nihon kohden RB 5) and were recorded on a photorecorder (Yokokawa electric EMO 62) at a paper speed of 20 cm per second The VCG s by Frank lead system were imaged on a vectorcardiograph (Fukuda electro VA 3D) and a picture was taken on a 35 mm film The VCG loops were interrupted at 2 5 msec intervals

Results

ECG patterns

1 Changes in left anterior subdivision block (LASB) and left anterior subdivision block combined with right bundle branch block (LASB combined with RBBB) The first ECG (Fig 3) shows a typical example of cutting the anterior subdivision of the left bundle branch alone and additionally cutting the main right bundle branch This control ECG pattern (left trac... seems similar to those of the human subject After cutting the anterior subdivision of the left bundle branch S waves in Leads II, III and V_1 increased in size LASB shifted $\bar{A}$ QRS from +11° to −51° and widened QRS duration from 72 to ... msec After adding RBBB to the existing LASB remarkable prolongation of QRS duration occurred (110 msec) and $\bar{A}$ QRS was shifted furthermore to −91° Wide S waves in Leads I II III and V_1 and a late R in Lead V_1 were observed

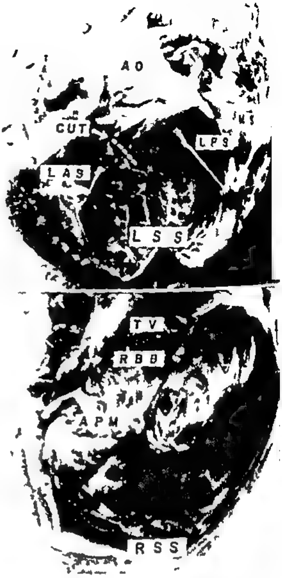
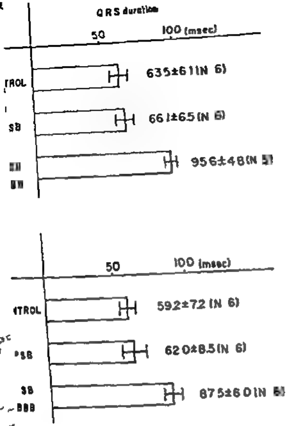


Fig 2 Shows the distribution of the canine intraventricular conduction system Above left septal surface below right septal surface

2 Changes in left posterior subdivision block



7 Changes of QRS duration before and after production ASB or LPSB and the combination of RBBB

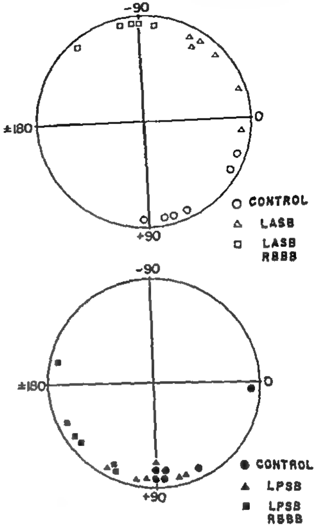


Fig 8 Changes of direction of the mean QRS axis.

77° ≃ +123°) but no significant changes were served statistically in comparison with the ntrol group After LPSB combined with RBBB lid squares) it rotated clockwise to an average +143.8 (range −167 ≃ +155°)

iscussion

There have been some experimental limitations the method used in animal experiments on indle branch block Therefore it seems to be ther difficult to correlate the experimental find with findings in man In the present study CG s and VCG s were recorded from the elec odes fixed on the surface of the torso model hich was designed to closely simulate the uman torso and moreover the validity of the rank lead system attached to the torso was dentified experimentally by measuring the lead ector and the lead system provided to have ufficient orthogonality and normality The QRS configurations obtained by this method were close to those of man Hence it may be partly possible to compare the experimental findings using this method with the clinical findings

Special attention should be paid in animal experiments on bundle branch block to reducing the injury against the ventricular muscle because the peripheral Purkinje fibers may have a great effect on ventricular excitation On this point we made the cutting at a particular site in the conduction system under direct visualization therefore the injury against the ventricular muscle was reduced to a minimum except the area of cutting in the septal surface Especially no damages were inflicted on the free ventricular wall

In 1968 Rosenbaum[1] classified the conduction disturbances of left bundle branch based on the site of injury in the conduction system According to his conclusion the left bundle branch is

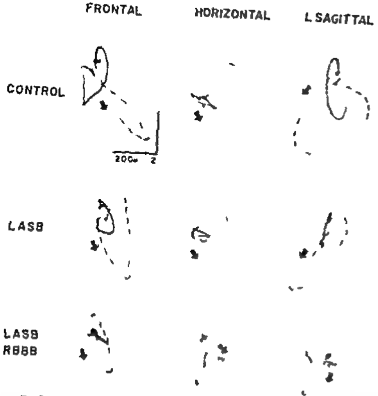


Fig 5 Typical VCG changes with LASB alone and after LASB combined with RBBB Upper control patterns middle with LASB lower after LASB combined with RBBB Each dot is tear shaped and shows the direction of rotation of QRS loop The blunt end of the dot leads the sharp end and each dot is written at intervals of 2 5 msec

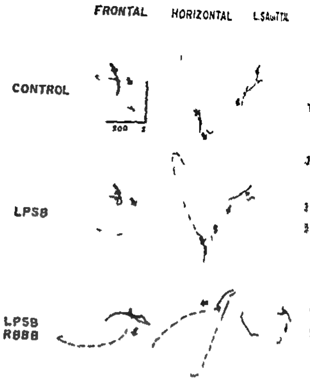


Fig 6 Typical VCG changes with LPSB alone and after LPSB combined with RBBB

loop is clockwise in the frontal plane counter clockwise in the left sagittal and horizontal planes With LPSB alone the main body and terminal portion of the QRS loop were displaced to the right and inferiorly, but the initial portion of QRS loop did not show any essential changes in direction The direction of rotation also showed no change A terminal delay was not observed After LPSB combined with RBBB the QRS loop showed a remarkable change The afferent limb of the QRS loop was displaced anterosuperiorly and to the right and a terminal delay was observed

In the following section all cases which were included in this series of experiments, particularly in relation to the QRS duration and the mean QRS axis are summarized

Changes in QRS duration The changes of QRS duration in 12 cases are summarized in Fig 7 The upper panel shows six cases of LASB alone and five cases of LASB combined with RBBB In the control group QRS duration ranged from 56 to 72 msec average 63.5 ± 6.1 ($n = 6$) With LASB alone it was prolonged from 58 to 76 msec average 66.1 ± 6.5 ($n = 6$), additional RBBB prolonged the QRS duration to an average of 95.6 ± 4.8 msec ($n = 6$)

The lower panel shows six cases of LPSB alone and LPSB combined with RBBB In the control group the QRS duration ranged from 48 to [illegible] msec average 59.2 ± 7.2 ($n = 6$) LPSB prolonged the QRS duration to an average of 62.0 ± 8.5 msec ($n = 6$), additional RBBB prolonged it further to an average of 87.5 ± [illegible] msec ($n = 6$) It is evident from Fig 7 that a very slight increase in the QRS duration was seen with LASB or LPSB but significant prolongation was observed after adding RBBB to the existing either LASB or LPSB

Changes in the direction of the mean QRS axis Fig 8 shows the changes of direction of the mean QRS axis in 12 cases The upper panel shows six cases of LASB alone and five cases of LASB combined with RBBB In the control group (open circles) the Â QRS was oriented inferiorly and to the left an average of +60.5 ($+21° \simeq +94°$) With LASB alone (open triangles) it deviated superiorly and to the left an average of $-35.8°$ ($-60° \simeq +90°$) After LASB combined with RBBB (open squares) the axis was further rotated counterclockwise to an average of $-99.8°$ ($-130° \simeq -82°$) The lower panel shows six cases of LPSB alone and LPSB combined with RBBB In the control group (solid circles) the axis was an average of +70.[illegible] ($+4° \simeq +90°$) With LPSB (solid triangles) it rotated clockwise to an average of +94.0°

We have evaluated the following histopatho ical study in the clinical diagnosis of hemi ck Some investigators[1] reported that the G pattern of LAH appeared to be related to ere alterations of the left bundle branch and areas of lesions involving the conduction tem were much more widely scattered not ited to the anterior subdivision Other investi tors also reported that no specific area of the nduction system was consistently involved By nsidering these facts it should be noticed that e changes in the initial part of the QRS are less portant in the diagnosis of hemiblock

In recent years bilateral bundle branch block s been generally accepted as the predominant use of complete heart block based on clinical id electrocardiographic studies The QRS itterns after we cut the left anterior subdivision id right bundle branch differed from the ones served in clinical practice Namely after itting the bilateral bundle branch the electrical xis was situated superiorly or superiorly to the ght In most cases in man which show LAD ombined with RBBB electrocardiographically he QRS axis would be situated superiorly and to he left This difference may be due to the gap in he origin of the conduction disturbance between iseases and experimental cutting The causes of he bundle branch block in clinical practice are leeding necro is fibrosis and anoxia of the issue whereas in experiments the block was nade by cutting a particular site in the conduc ion system Accordingly there may be some differences in the mode of excitation of the ventricle between the cases of disease and experi mental cutting in animals It is interesting that the QRS pattern observed in our experiment closely resembled the postsurgical ECG changes in ventricular septal defect and te tralogy of Fallot These coincidences of the ECG changes may result from a common origin of the conduction disturbance Alternatively the mode of activation after surgical treatment could be identical with the one in experimental cutting

On the other hand the QRS pattern after cut ting the left posterior subdivision and addition ally the main right bundle branch showed a RAD + RBBB configuration This ECG change resem bled that of LPSB combined with RBBB in clinical practice However the QRS pattern after cutting only the main right bundle branch showed also a striking resemblance to this ECG change A typical case is shown in Fig 9 This may be due to the difference in the mechanism between experimental RBBB and clinical RBBB

The introduction of the concept of hemiblock in conduction disturbances is simple to apply and also of clinical value Our results provide experi mental support for this concept but minor find ings are discordant with the conclusion of Rosen baum and associates[1] [2] Further studies will be necessary to better understand the mechanism of hemiblock

Summary

ECG and VCG changes in QRS configuration before and after left anterior subdivision block (LASB) isolated and combined with right bundle branch block (LASB combined with RBBB) were studied in canine hearts In another series left posterior subdivision block (LPSB) isolated and combined with right bundle branch block (LPSB combined with RBBB) were also per formed

With LASB the $\bar{A}$ QRS axis deviated superi orly to the left and the QRS duration showed no significant prolongation Additional RBBB to the existing LASB moreover rotated the $\bar{A}$ QRS axis counterclockwise and prolonged the QRS dura tion significantly

With LPSB the axis was deviated inferiorly to the right and the QRS duration showed no signif icant prolongation Additional RBBB to the ex isting LPSB rotated the $\bar{A}$ QRS axis clockwise The QRS duration showed significant prolonga tion

Vectorcardiographically the initial part of the QRS loop did not show any essential changes with either LASB or LPSB The main and terminal parts of the QRS loop however were deviated superiorly and to the left with LASB and inferiorly and to the right with LPSB No changes were observed in the direction of rotation of QRS loop with either subdivision block From these results it appears that the changes in the terminal forces are more of importance than the initial forces in the diagnosis of hemiblock

The author would like to thank sincerely Prof Kazuo Yamada and Assoc Prof Junji Toyama for their most helpful interest and for the opportunity to perform this study in their department The author also wishes to thank Prof David H Spodick for his careful review of the manuscript and Drs. Toshiyo Kobayashi, Atsushi Ito and Hajime Oguri for their helpful advice

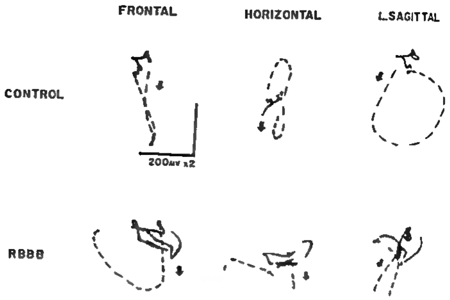


Fig 9 Typical VCG changes after production of RBBB

composed of a main stem and two subdivisions (anterior and posterior subdivisions), going to the two papillary muscles of the left ventricle, and consequently these two subdivisions can be independently damaged He has designated such damage as left anterior hemiblock (LAH) and left posterior hemiblock (LPH) respectively

On the other hand Demoulin and Kulbertus[18] reported from their pathological study on the subdivisions of the left bundle branch that the left sided Purkinje system appears to constitute three rather than two, main peripheral networks This view was supported by Uhley[19] and Durrer and associates [20] Lazzara and associates[21] furthermore stated that the left bundle branch is best represented as a fan shaped structure Thus there is a disagreement among investigators concerning the distribution of the left bundle branch and it has not yet been clearly defined Therefore, it is worthwhile to reconsider the distribution and course of the left bundle branches, because the distribution of the intraventricular conduction system seemed to be one of the most pending factors which could possibly influence the direction of the initial forces

According to our observations, the direction of the initial part of QRS showed no significant changes with cutting either the anterior or posterior subdivision of the left bundle branch and most remarkable changes were observed in the terminal portion of the QRS The finding may be explained as follows First, the left bundle branch is regarded as a trifascicular system or a fan shaped structure, rather than a bifascicular system, so that the interconnection among the subdivided fascicles may be abundant Hence it is rather difficult to determine, without reserve and qualification, the direction of the initial forces Second it may be also partly explained by the site of cutting of the conduction system The cutting was made at the level of the middle third of the distance to the anterior or posterior papillary muscle

In other words, the sites of cutting were so distal in the left bundle branch that the initial part of the QRS could not show any significant change The study by Fernandez and associates provided a clinical support for our observations They observed that the QRS changes during coronary arteriography showed patterns close to hemiblock These changes were not accompanied by any significant modification of the initial forces Consequently they emphasized the importance of deviation of terminal forces rather than deviation of initial forces On this point, however Rosenbaum and associates[23] re emphasized the changes of the initial part of the QRS forces in the diagnosis of hemiblock based on the observations in which the ECG changes induced by catheterization of the left ventricular outflow tract were compared with those induced during coronary arteriography That is, the axis shift occurring in the former induced a change in the initial forces which become oriented inferiorly and to the right Yet the one occurring in the latter showed no changes in the initial forces, they then concluded that an axis shift in the absence of changes in the initial forces may be due to the conduction disturbance not in the Purkinje tissue but in the myocardium

pranolol ın experımental myocardıal ıemıa Dıssocıatıon of effects on contractıon l epıcardıal ST segments

ıty M Bodenheımer M D
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ısiderable recent ınterest has focused on empts to lımıt the extent of myocardıal ıemıc ınjury durıng the perıod ımmedıately owıng coronary occlusıon [1, 2] Propranolol has n suggested as a possıble means of reducıng ıte ıschemıc ınjury and thus potentıally ıservıng myocardıal tıssue In thıs regard ent studıes have ındıcated that myocardıal tabolısm ımproves ın patıents treated wıth opranolol.[4] Experımental and clınıcal[7, 8] ıdıes, however have demonstrated sıgnıficant pressıon of myocardıal functıon by propranolol the presence of acute myocardıal ıschemıa The fferentıal effect of propranolol on regıonal ntractıle functıon of the ıschemıc and border nes followıng coronary occlusıon has not been aluated. The present study was therefore ndertaken to examıne the effect of thıs agent on oth the degree of ıschemıc ınjury and zonal ontractıle performance

Methods

Studıes were performed ın ■ mongrel dogs weıghıng 25 to 30 kılograms and anesthetızed wıth sodıum pentobarbıtal (30 mg per kılogram ıntravenously) and ventılated wıth a Harvard respırator The heart was exposed through a mıdsternal ıncısıon and supported ın a perıcardıal radle A polyethylene tube was ıntroduced through an ınternal jugular veın for ıntravenous ınfusıon Central aortıc pressure was monıtored wıth a P23Db transducer and a wıde bore stıff catheter ıntroduced through the rıght common carotıd artery Fıne Teflon coated staınless steel pacıng wıres were ıntroduced ınto the rıght atrıum vıa 25 gauge needles to achıeve rate control by atrıal pacıng

The left anterıor descendıng coronary artery was ısolated 2 to 3 cm dıstal to ıts orıgın The potentıally ıschemıc and nonıschemıc zones were demarcated wıth epıcardıal electrograms and confirmed wıth methylene blue at the conclusıon of each study as prevıously descrıbed [1, 2] Walton Brodıe straın gauge arches of 120 ohm resıstance wıth adjustable feet were fixed wıth deep sutures ın the potentıally ıschemıc border and nonıschemıc zones The myocardıal segment under the two feet of each straın gauge arch was stretched by 30 per cent of ıts ınıtıal length

Epıcardıal electrograms were obtaıned wıth sılver electrodes of 2 mm dıameter mounted ın acrylıc plastıc Ten to 12 electrodes were applıed to the myocardıal surface and kept ın place wıth a sılk thread runnıng over the plastıc bars and stabılızed vıa the rıght and left sıdes of the perıcardıum No epıcardıal sutures were used Thıs permıtted the electrodes to be kept ın a fixed posıtıon throughout each experıment whıle avoıdıng pressure on the myocardıum whıch could result ın ST segment changes All epıcardıal recordıngs were obtaıned at a sensıtıvıty of 1 mm per mıllıvolt and frequency lımıts of 0 1 to 100 Hz Standard (electrocardıogram)(ECG) Lead II was also monıtored throughout each experıment All records were taken on a multıchannel oscılloscopıc recorder (Electronıcs for Medıcıne) at paper speeds of 25 and 100 mm per second After control recordıngs were obtaıned coronary occlu

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REFERENCES

1. Benchimol, A Barreto E C and Pedraza A The Frank vectorcardiogram in left anterior hemiblock J Electrocardiol 4 116 1971
2. Benchimol A and Desser K B The Frank vectorcardiogram in left posterior hemiblock J Electrocardiol 4 129 1971
3. Lemberg L Castellanos A and Arcebal A G The vectorcardiogram in acute left anterior hemiblock Am J Cardiol 28 483 1971
4. Kulbertus H Collignon P and Humblet L Vector cardiographic study of the QRS loop in patients with left anterior focal block AM HEART J 79 293 1970
5. Medrano G A Brenes C Micheli A D and Sodi Pallares D Clinical electrocardiographic and vectorcardiographic diagnosis of the left anterior subdivision block isolated or associated with RBBB AM HEART J 83 447 1972
6. Varriale P and Kennedy R J Right bundle branch block and left posterior fascicular block vectorcardiographic and clinical features Am J Cardiol 29 459 1972
7. Schweitzer P Mellen H S and Rubenfire M Left posterior hemiblock J Electrocardiol 4 204 1971
8. Lopes V M Miguel M [illegible] Reis D D Costa C B and Padua F Left posterior hemiblock clinical and vector cardiographic study of twenty cases J Electrocardiol 7 197 1974
9. Fernandez F Scebat L and Lenegre J Electrocardiographic study of left intraventricular hemiblock in man during selective coronary arteriography Am J Cardiol 26 1 1970
10. Rosenbaum M B Types of right bundle branch block and their clinical significance J Electrocardiol 1 221 1968
11. Rosenbaum M B Elizari M V Lazzari J O Nau G J Levi R J and Halpern M S Intraventricular trifascicular blocks Review of the literature and classification AM HEART J 78 450 1969
12. Rosenbaum M B Types of left bundle branch block and their clinical significance J Electrocardiol 2 197 1969
13. Rosenbaum M B The hemiblocks diagnostic criteria and clinical significance Mod Concepts Cardiovasc Dis 39 141 1970
14. Uhley H N and Rivkin L M Electrocardiographic patterns following interruption of the main and peripheral branches of the canine left bundle of His Am J Cardiol 13 41 1964
15. Watt, T B Freud G E Durrer D and Pruitt R D Left anterior arborization block combined with right bundle branch block in canine and primate hearts Circ Res. 22 57 1968
16. Watt T B and Pruitt R D Electrocardiographic findings associated with experimental arborization block in dogs AM HEART J 69 642 1965
17. Medrano G A Micheli, A Cisneros, F and Sodi Pallares, D The anterior subdivision block of the left bundle branch of His II Experimental vectorcardiographic observations, J Electrocardiol. 3 [illegible]
18. Demoulin J C and Kulbertus, H. E Histopathological examination of concept of hemiblock, Br Heart J 34 807 1972
19. Uhley H N Some controversy regarding the peripheral distribution of the conduction system Am. J Cardiol 30 919 1972
20. Durrer D Dam T, Freud G E Janse M J [illegible] F I and Arzbaecher R. C Total excitation of the isolated human heart Circulation 41 899 1970
21. Lazzara R Yeh B K and Samet, P Functional anatomy of the canine left bundle branch, Am J Cardiol 33 623 1974
22. Lev M The normal anatomy of the conduction system in man and its pathology in atrioventricular block. [illegible] N Y Acad. Sci. 3 817 1964
23. Rosenbaum M B Shabetai, R Peterson K L and Orourke R A Nature of the conduction disturbance [illegible] selective coronary arteriography and left heart catheterization Am J Cardiol 30 334 19[illegible]
24. Entman M L Estes, E H Hackel D B and [illegible] N C The pathologic basis of the electrocardiographic pattern of parietal block, AM HEART J 74 [illegible]
25. Scanlon P J Pryor R and Blunt S G Right bundle branch block associated with left superior or [illegible] intraventricular block Clinical setting prognosis [illegible] relation to complete heart block Circulation 42 [illegible] 1970
26. Downing J W Kaplan S and Bove K E [illegible] gical left anterior hemiblock and right bundle branch block Br Heart J 34 263 1972.
27. Chesler E Beck W and Schrire V Left anterior hemiblock and right bundle branch block before and after surgical repair of tetralogy of Fallot, AM HEART J 84 45 1972
28. Gelband H Waldo A L Kaiser G A Bowman F [illegible] Malm J R and Hoffman B F Etiology of right bundle branch block in patients undergoing total correction of tetralogy of Fallot Circulation 44 1022, 19[illegible]
29. Titus, J L Daugherty G W Kirklin, J W and Edwards, J E Lesions of the atrioventricular conduction system after repair of ventricular septal defect Circulation 28 82 1963
30. Muraki H Dextrocardiogram levocardiogram and septocardiogram as obtained by cutting away of [illegible] ventricular free walls of the perfused canine heart, Jap Circ J 31 995 1967
31. Yamada K. Okajima M Hori, K Toyama J Koyashi T Fujino T and Muraki H Electro and vectorcardiograms of perfused canine heart immersed in electrolyte-filled human torso model Jap Heart J 7 [illegible] 1966

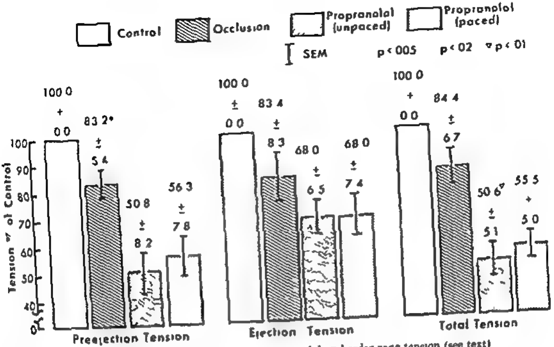

Fig. 2 Effect of coronary occlusion and propranolol on border zone tension (see text)

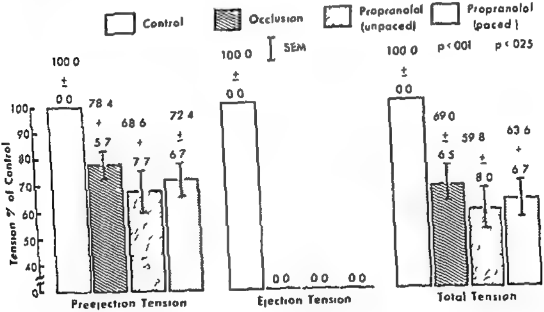

Fig 3 Effect of coronary occlusion and propranolol on ischemic zone tension (see text)

ant improvement in these parameters occurred Fig 1)

In the border zone total tension decreased to 84 4 ± 6 7 per cent ($p < 0.02$) following coronary occlusion with similar changes in pre ejection and ejection tension (Fig 2) After propranolol total tension decreased sharply from 84 4 ± 6 7 to 50 6 ± 5 1 per cent ($p < 0.01$) with parallel changes in pre-ejection and ejection tension (Fig 2) When pacing was instituted no significant changes were seen

Ischemic zone tension (Fig 3) decreased

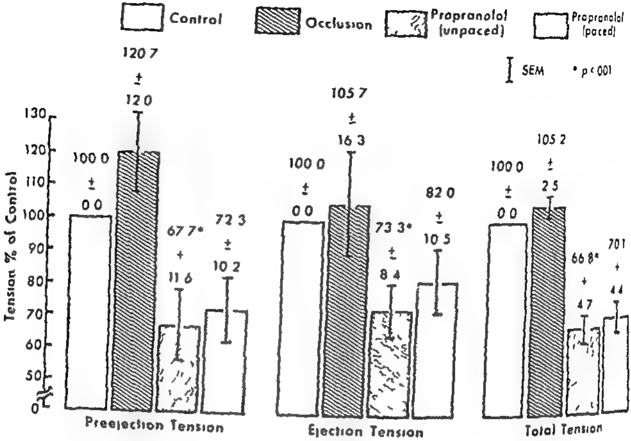

Fig 1 Effect of coronary occlusion and propranolol on nonischemic zone tension (see text)

sion was performed with a rubber covered clamp A period of 30 minutes was permitted for stabilization of contractile changes and rhythm disturbances Following the postocclusion recordings propranolol (1 mg per kilogram) was given as a bolus This dosage prohibited isoproterenol (0.1 mg per kilogram per minute) from eliciting a characteristic response when infused at the end of each experiment as previously described[1] After 10 minutes recordings were again taken following which atrial pacing at a rate equal to the post-coronary occlusion, prepropranolol level was instituted A period of 5 minutes was allowed for stabilization and the recordings were repeated

Tension parameters including pre ejection tension, ejection tension and total tension were analyzed as per cent of preocclusion levels[11] The ST segments were analyzed for total (ΣST) and average ST elevation (S T) ST elevation $\geq$ 2 mv was considered indicative of myocardial ischemia In no case was ischemic ST elevation present prior to coronary occlusion

Student's t test for paired data was utilized for statistical analyses All values are given as mean $\pm$ S E M (standard error of the mean)

Results

After coronary occlusion heart rate increase[d] slightly from 159.7 ± 5.3 to 165.0 ± 3.5 beats pe[r] minute ($p < 0.05$) without a significant chang[e] in blood pressure (systolic $110.5 \pm 4.$ to 112.7 ± 4.1 mm Hg, diastolic, 91.1 ± 3.9 to 88.4 ± 4.0 mm Hg) Following the infusion of propranolol heart rate decreased from 165.0 ± 3.5 to 126.2 ± 4.7 beats per minute ($p < 0.001$) while both the systolic and diastolic blood pressures remained unchanged (112.7 ± 4.1 to 113.8 ± 6.3 mm Hg 88.4 ± 4.0 to $91.1 \pm 4.$ mm Hg) These changes stabilized after 5 minutes No significant change occurred in blood pressure after the heart rate was restored to prepropranolol levels

1 Tension parameters Following coronary occlusion no significant changes were observed in the nonischemic zone (Fig 1) Propranolol however reduced all tension parameters sharply Pre ejection tension decreased from $120.7 \pm 12.$ to 67.7 ± 11.6 per cent ($p < 0.001$), ejection tension from 105.7 ± 16.3 to 73.3 ± 8.4 per cent ($p < 0.001$) and total tension from $105.2 \pm$ per cent to 66.8 ± 4.7 per cent ($p < 0.001$) When the heart rate was restored by pacing no signifi

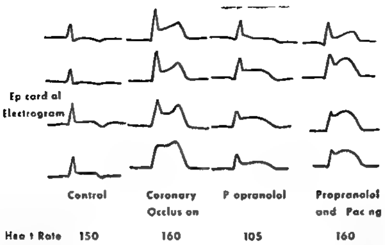

Fig 6 A typical experiment showing the effect of coronary occlusion and propranolol on epicardial ST segments. Following coronary occlusion there is marked ST elevation Propranolol administration results in a significant decrease in ST elevation coincident with the decrease in heart rate When atrial pacing is instituted during the propranolol effect the ST segments again become elevated

i previous observations that ischemic injury measured by ST segments is reduced signifi ntly by propranolol administration This effect pears to be dependent in major part on the duction in heart rate (Figs 5 and 6) since when e negative chronotropic effect was eliminated th pacing the beneficial effects of propranolol ifusion on ischemic injury were lost

The depression in local segmental function which occurs in the nonischemic border and schemic zones with propranolol further suggests hat the previously described decrease in ventric ilar function during beta blockade is a result of eneral depression of the entire myocardium A revious study in patients with stable coronary rtery disease also indicated that propranolol nay worsen segmental contraction depicted entriculographically Unfortunately it does not appear that segments of myocardium with differing degrees of ischemia show a differential response to propranolol that is one cannot demonstrate improved contractile ability of the border or ischemic zone despite the apparent improvement in ischemia as measured by ST segment elevation This is consistent with the decrease in cardiac function despite improved ST segments recently described by Gold and associates

Thus propranolol appears to improve myocardial oxygen supply demand relationships at least in part related to the reduction in heart rate To achieve this beneficial effect however a considerable reduction in contractile function is produced If these experimental observations are applicable to the clinical setting it suggests that the usefulness of propranolol may be limited

Summary

Recent studies have suggested that propranolol decreases the extent of myocardial injury in acute ischemia Although other studies have shown that global myocardial performance is depressed zonal effects of propranolol in this setting are unknown Therefore the effect of propranolol (1 0 mg per kilogram) was investigated in nine dogs with the use of Walton Brodie strain gauge arches and local epicardial electrograms (10 to 12 sites) The heart rate effects of propranolol were controlled by atrial pacing After coronary occlusion heart rate increased slightly without a significant change in blood pressure Following the infusion of propranolol heart rate decreased significantly from $165\ 0 \pm 3\ 5$ to $126\ 2 \pm 4\ 7$ beats per minute ($p < 0\ 001$) while both the systolic and diastolic blood pressures showed insignificant changes After coronary occlusion nonischemic zone tension showed no significant changes however propranolol decreased total tension from $10 5\ 2 \pm 2\ 5$ per cent to $66\ 8 \pm 4\ 7$ ($p < 0\ 001$) Similarly propranolol further decreased total tension in the border zone from $84\ 4 \pm 6\ 7$ per cent ($p < 02$) to $50\ 6 \pm 5\ 1$ ($p < 0\ 01$) Ischemic zone tension also fell further ($p < 0\ 025$) after propranolol Restoration of prepropranolol heart rate had no significant effect on tension development

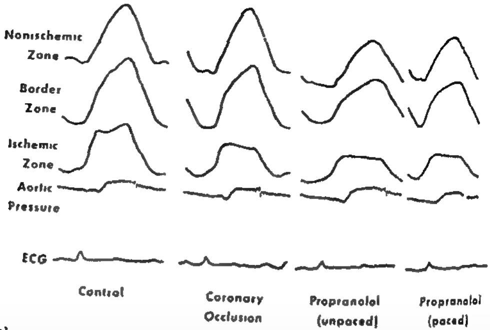

Fig 4 A typical experiment demonstrating the effect of coronary occlusion and propranolol on zonal tension development Following coronary occlusion nonischemic zone tension is unaffected Border zone tension decreases significantly and the ischemic zone contractile force shows a marked loss in both pre ejection and ejection tension After propranolol administration further significant decreases in tension development are seen in all three zones with no improvement when atrial pacing at prepropranolol rate is instituted

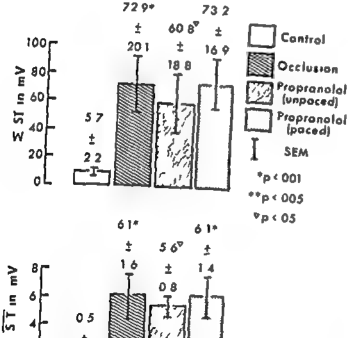

Fig 5 Effect of coronary occlusion and propranolol on epicardial ST segments ΣST = Total ST elevation S T = average ST elevation

sharply following coronary occlusion and similarly to the nonischemic and border zones a further significant ($p < 0\,025$) decrease in pre ejection and total tension occurred with propranolol Restoration of heart rate again had no significant effect

Fig 4 represents a typical experiment illustrating these changes in tension development

2 ST segments Following coronary occlusion ΣST increased from 5 7 ± 2 2 to 72 9 ± 20 1 mv ($p < 0\,001$) and S T from 0 5 ± 0 1 to 6 1 ± 1 6 mv ($p < 0\,001$) (Fig 5) Coincident with the negative chronotropic effect of propranolol and the decline in tension, ΣST decreased from 72 9 ± 20 1 to 60 8 ± 18 8 mv ($p < 0\,05$) and S T from 6 1 ± 1 6 to 5 6 ± 0 8 mv ($p < 0\,05$) When the heart rate was increased to prepropranolol levels ΣST again rose to 73 2 ± 16 9 mv ($p < 0\,005$) and S T to 6 1 ± 1 4 mv ($p < 0\,005$)

Typical changes in epicardial ST segments are illustrated in Fig 6

Discussion

Considerable recent attention has focused on decreasing the degree of myocardial injury[1,2] The ability of propranolol to decrease heart rate and myocardial contractility should favorably reduce myocardial oxygen consumption The improvement induced by propranolol in ST segments[3] and metabolic indices[4] is consistent with this finding Controlled trials of propranolol in the early post-myocardial infarction period, however have failed to show significant improvement in the treated group[7,8]

The findings of the present study are consistent

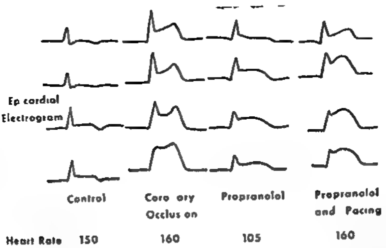

Fig 6 A typical experiment showing the effect of coronary occlusion and propranolol on epicardial ST segments Following coronary occlusion there is marked ST elevation Propranolol administration results in a significant decrease in ST elevation coincident with the decrease in heart rate When atrial pacing is instituted during the propranolol effect the ST segments again become elevated

h previous observations that ischemic injury measured by ST segments is reduced signifi ntly by propranolol administration This effect pears to be dependent in major part on the duction in heart rate (Figs 5 and 6) since when e negative chronotropic effect was eliminated th pacing the beneficial effects of propranolol fusion on ischemic injury were lost

The depression in local segmental function hich occurs in the nonischemic border and chemic zones with propranolol further suggests at the previously described decrease in ventric lar function during beta blockade[5] is a result of eneral depression of the entire myocardium A revious study in patients with stable coronary rtery disease also indicated that propranolol ay worsen segmental contraction depicted entriculographically Unfortunately it does not ppear that segments of myocardium with iffering degrees of ischemia show a differential esponse to propranolol that is one cannot lemonstrate improved contractile ability of the border or ischemic zone despite the apparent improvement in ischemia as measured by ST segment elevation This is consistent with the decrease in cardiac function despite improved ST segments recently described by Gold and asso ciates

Thus propranolol appears to improve myocar dial oxygen supply demand relationships at least in part related to the reduction in heart rate To achieve this beneficial effect however a consid erable reduction in contractile function is produced If these experimental observations are applicable to the clinical setting it suggests that the usefulness of propranolol may be limited

Summary

Recent studies have suggested that propranolol decreases the extent of myocardial injury in acute ischemia Although other studies have shown that global myocardial performance is depressed zonal effects of propranolol in this setting are unknown Therefore the effect of propranolol (1 0 mg per kilogram) was investigated in nine dogs with the use of Walton Brodie strain gauge arches and local epicardial electrograms (10 to 12 sites) The heart rate effects of propranolol were controlled by atrial pacing After coronary occlu sion heart rate increased slightly without a significant change in blood pressure Following the infusion of propranolol heart rate decreased significantly from 165 0 ± 3 [illegible] to 126 [illegible] ± 4 7 beats per minute ($p < 0\,001$) while both the systolic and diastolic blood pressures showed insignificant changes After coronary occlusion nonischemic zone tension showed no significant changes however propranolol decreased total tension from 105 2 ± 2 5 per cent to 66 8 ± 4 7 ($p < 0\,001$) Similarly propranolol further de creased total tension in the border zone from 84 4 ± 6 7 per cent ($p < 02$) to 50 6 ± 5 1 ($p < 0\,01$) Ischemic zone tension also fell further ($p < 0\,025$) after propranolol Restoration of prepropranolol heart rate had no significant effect on tension development

Following coronary occlusion, ΣST increased from 5.7 ± 2.2 to 72.9 ± 20.1 mv ($p < 0.001$). Coincident with the decrease in heart rate and tension development induced by propranolol, ΣST decreased to 60.8 ± 18.8 mv ($p < 0.05$). When the heart rate was restored to prepropranolol level, ΣST again rose to 73.2 ± 16.9 mv ($p < .005$).

Thus, propranolol does effect an improvement in ischemic injury which is related, at least in part, to the induced decrease in heart rate. A concomitant substantial decrease in local tension development also occurs, however. The latter observations may limit the potential usefulness of propranolol in this setting.

We wish to thank Mr. Joseph Lewankowski and Miss Janice Phillips for their technical assistance and Ms. Marcy Moore and Miss Jeanne Harrison for their secretarial assistance.

REFERENCES

1. Sobel B E and Shell W E Jeopardized blighted and necrotic myocardium Circulation 47 215 1973
2. Maroko P R and Braunwald E Modification of myocardial infarction size after coronary occlusion Ann Intern Med 79 720 1973
3. Maroko P R Kjekshus J K Sobel B E Watanabe T Covell J W Ross J Jr Braunwald E Factors influencing infarct size following experimental coronary artery occlusion Circulation 43 67 1971
4. Mueller H S Ayres S M Religa A and Evans R G Propranolol in the treatment of acute myocardial infarction Effect on myocardial oxygenation and hemodynamics, Circulation 49 1078, 1974
5. Liang C S and Hood W B The myocardial depressant effect of beta receptor blocking agents, Circ Res 35 272 1974
6. Stein P D Brooks H L Matson J L and Hyland J W Effect of beta adrenergic blockade on coronary blood flow Cardiovasc. Res. 2 63 1968
7. A Multicentre Trial Propranolol in acute myocardial infarction Lancet 2 1435 1966
8. Balcon R Jewitt D E Davies, J P H and Oram S A controlled trial of propranolol in acute myocardial infarction Lancet 2 917 1966
9. Amsterdam E A Hilliard G Williams, D O Cain C Vismara L Massumi R A and Mason, D T Hemodynamic effects of propranolol in acute myocardial infarction (abst.) Circulation 48 IV 138, 1973
10. Gold H K Leinbach, R C and Maroko, P R Reduction of myocardial injury in patients with acute infarction by propranolol (abst.) Circulation 49 III 31 1974
11. Banka V S and Helfant, R H Temporal sequence of dynamic contractile characteristics in ischemic and nonischemic myocardium after acute coronary ligation Am J Cardiol 34 158 1974
12. Banka V S Chadda K D and Helfant, R H Limitations of myocardial revascularization in restoration of regional contraction abnormalities produced by coronary occlusion Am J Cardiol 34 164 1974
13. Nakano J and Kusakari T Effect of beta blockade on the cardiovascular dynamics Am J Physiol 210 833 1966
14. Helfant R H Herman M V and Gorlin R Abnormalities of left ventricular contraction induced by beta adrenergic blockade Circulation 43 641 1971

...diovascular effects of ajmaline

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...aline which was first isolated in 1932 is a ...ative of the Indian plant *Rauwolfia serpen...* It is a member of a second class (ajmaline ...p) of rauwolfia derivatives which have no ...tive hypnotic tranquilizing or hypotensive ...ts. In 1956 Arora and Madan first reported ... ajmaline a tertiary indolin base had potent ...tiarrhythmic effects Subsequent reports have ...urly confirmed the efficacy of ajmaline as an ...tiarrhythmic agent for atrial and ventricular ...rhythmias[3] Furthermore it has proved to be ...remely successful in the treatment of arrhyth...s in patients with the Wolff Parkinson White ...drome However little information is avail...e concerning the hemodynamic and electro...ysiologic effects of this drug Therefore this ...dy was designed to elucidate more clearly the ...diovascular effects of ajmaline

...ethods

I Hemodynamic studies

A Anesthetized dogs Seven mongrel dogs ...selected by age or sex with weights ranging ...om 20 to 34 kilograms were anesthetized with ...travenous sodium pentobarbital (20 to 30 mg ... kilogram) A tracheostomy was performed and the tracheal cannula was connected to a Harvard pump for positive pressure breathing with room air A transthoracic incision was made between the fourth and fifth ribs The pericardium was incised and the left anterior descending coronary artery exposed A pulsed field electromagnetic flowmeter probe was placed around the left anterior descending coronary artery A flowmeter probe was also placed around the proximal ascending aorta and pulmonary artery to measure left and right ventricular output

A femoral artery was cannulated with a Teflon cannula which in turn was connected to a P23AA Statham pressure transducer in all dogs the cannula was threaded to the root of the aorta for central aortic pressure measurements A second catheter was introduced into the left ventricle to permit measurements of left ventricular pressures The flowmeter probes were connected to electromagnetic flowmeters and calibrated as previously described [3] Flow levels and computer readings strain gauge pressure and Lead II of the electrocardiogram (ECG) were recorded on a multichannel photographic recorder (Model DR 16 Electronics for Medicine) The femoral vein was also cannulated for fluid administration After obtaining control readings in duplicate 5 minutes apart to insure steady state ajmaline was administered in a single intravenous bolus at incremental doses of 0 25 0 5 1 0 2 0 4 0 and 8 0 mg per kilogram Regional flow and pressure levels were recorded 5 and 15 minutes after drug administration The flow

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results were obtained from integrating the data from the electromagnetic flowmeter for a period of 60 seconds However the instantaneous flow was also recorded to correlate and assess factors that affect phasic blood flow and to insure that the computer was not integrating spurious results Subsequent increases in ajmaline dose was administered only after a minimum of 20 minutes or when the recorded values returned to control Statistical comparison of these data was obtained by an analysis of the mean percentage change from control values by paired Student s t test

B Conscious dogs With the use of a previously described technique[13] polyvinyl chloride catheters were implanted for chronic use so that the following pressures could be recorded central aortic, right ventricular pulmonary artery and right atrial After an appropriate training period dogs were able to maintain the upright position supported by a Pavlovian sling for periods of up to 4 hours without any significant change in the hemodynamic measurements and/or heart rate Studies were performed with this preparation in five dogs After controlled recordings were obtained in duplicate a minimum of 5 minutes apart ajmaline was administered as an intravenous bolus into the right atrium in increasing doses of 0 25 0 5 1 0, 2 0 and 4 0 mg per kilogram Recordings were made of the various pressures 5 minutes after injection After return to baseline levels, additional doses were given as outlined above Cardiac outputs were also obtained during each drug administration sequence with the indicator dilution technique (indocyanine green)

C In vitro studies Cats were anesthetized with 40 mg per kilogram of sodium pentobarbital intraperitoneally With methods previously described[14] right ventricular papillary muscles and isolated right atria were rapidly removed placed in a Krebs bicarbonate solution at 30° C and gassed with 95 per cent oxygen and 5 per cent carbon dioxide Each atrium spontaneously contracted while each papillary muscle was stimulated at 12 per minute by platinum mass electrodes at a voltage 10 per cent above threshold Isometric force was recorded (Hewlett Packard FTA 100 1 strain gauge) at the top of the length tension curve After 2 hours of equilibration cumulative dose response curves were obtained with the addition of ajmaline to achieve concentrations of from 10^{-8} to 10^{-3} M

II Electrophysiologic studies In dogs we[…] 18 to 25 kilograms five different series of ex[…]ments were performed to ascertain the fo[…] electrophysiologic properties of ajmaline […] effects on AV conduction time in normal d[…] effects on AV conduction time in digitali[…]cated dogs (3) effects on ventricular autom[…] in normal and digitalized dogs, (4) effe[…] ischemic arrhythmias in conscious dogs, and […] effects on cardiac conduction in conscious d[…] In experiments 1 to 3, dogs were initially gi[…] morphine sulfate (3 mg per kilogram s[…]neously) followed in 30 minutes by ur[…] (1 to 3 Gm intravenously) and pentobarb[…] mg per kilogram intravenously

A Effects on AV conduction His bundle el[…]trograms were recorded with a 6F bipolar p[…] catheter introduced by the femoral vein a[…] fluroscopically positioned across the septal l[…] of the tricuspid valve Simultaneous ECG l[…] were recorded for reference

Pacing was performed via a 6F pacing cath[…] introduced from the jugular venous system w[…] was positioned at the superior vena caval ri[…] atrial junction High right atrial electrogra[…] were recorded with an additional catheter advanced to the right atrial–superior vena c[…] junction Atrial pacing was performed in […] control state of the experiments at rates of […] 130 150 170 190, and 210 per minute w[…] Tektronix stimulation and isolation units […]ulus characteristics were intensity 1 5× dia[…] threshold and a duration of 2 msec Mea[…]ments of SH (stimulus to His interval) time H[…] time and QRS duration were performed wi[…] standard techniques records were obtained a[…] 100 mm per second paper speed After cont[…] recordings were obtained seven dogs were giv[…] ajmaline intravenously every 20 minutes in step[…]wise fashion in doses of 0 25 0 5 1 0 2 0 and 4[…] mg per kilogram At the end of the test period repeat measurements were obtained Compari[…]sons were made only of records obtained at the same heart rate throughout the total experime[…] the heart rate chosen was the slowest paced ra[…] at which data could be plotted for all test dos[…] Four of these seven dogs had a right sided va[…]gotomy and in three dogs the vagi were intact

B Effects on digitalis intoxication Digital[…] intoxication was produced in six dogs by admin[…]tering an intravenous bolus of 7 5 μ per kilogra[…] of ouabain followed by a continuous ouabain

ᾹI Effects of ajmaline in seven open chest dogs (mean ± S E M)

	Control	0.25 mg/kg 5 min	0.25 mg/kg 15 min	0.5 mg/kg 5 min	0.5 mg/kg 15 min	1 0 mg/Kg 5 min	1 0 mg/Kg 15 min	2 0 mg/kg 5 min	2 0 mg/kg 15 min	4 0 mg/kg 5 min	4 0 mg/kg 15 min	8 0 mg/kg 5 min	8 0 mg/kg 15 min
rate (beats/)	140 ±8	144 ±8	144 ±7	144 ±8	14 ±7	142 ±8	144 ±8	1?8 ±10	144 ±10	119 ±10	127 ±12	67† ±9	71† ±12
arterial blood pressure (mm Hg)	109 ±5	113 ±5	116 ±5	112 ±6	112 ±6	112 ±5	115 ±5	114 ±4	117 ±4	102 ±6	108 ±5	45† ±8	62 ±10
max dP/dt (mm Hg/sec.)	2,1?0 ±?36	?,??7 ± 34	2,2 5 ±213	2 3 2 ±198	2 322 ±?11	2 23? ±197	2 161 ±193	2 135 ±?46	2 160 ±2?1	1 ?42 ±233	1 897 ±23?	71?† ±1?2	519† ±212
?DP (mm Hg)	8 9 ±1 4	9 3 ±?0	9 4 ±1 7	10 6 ±1 8	9 3 ±1 7	10 1 ±2 0	10 0 ±2 0	12 6 ±1 9	11 4 ±2 0	15 1 ±2 3	14 4 ±2 1	17.9† ±1 8	17 5† ±2.1
? index (ml / beat/M)	11 8 ±1 8	12 2 ±1 8	1?2 ±1 3	12 6 ±1 6	12 9 ±1 6	12 6 ±1 6	11 8 ±1 3	11 8 ±1 4	11 3 ±1 5	11 5 ±1 4	10 8 ±1 3	10.3 ±2.2	12.2 ±1 4
? work index (? m. m/beat/)	16 2 ±?4	17 1 ±?3	17 ±1 8	16 9 ±1 9	18 0 ±2 3	17 3 ±2 1	16 9 ±2 0	16 6 ±??	16 3 ±2 4	13 8 ±2 4	13 9 ±1.9	5 4 ±2 8	7 6 ±2.5
?iac index (L./ ?n /M.)	1 6 ±0 2	1 6 ±0 2	1 ? ±0 1	1 7 ±0 2	1 8 ±0 2	1 7 ±0 2	1 6 ±0 1	1 6 ±0.2	1.5 ±0 2	1.3 ±0 2	1 3 ±0 2	0 ±0 1	0 8 ±0 1
?emic vascular ?istance (10 ?ynes cm sec)	6 55 ±0 99	6 39 ±0 81	6 2? ±0 3	6 00 ±0 6?	5 74 ±0 80	6 12 ±0 91	6 47 ±0 91	6 8 ±1 03	7 35 ±1 33	7 34 ±1 2?	7 ?2 ±1 15	6 28 ±0 73	6 ?1 ±0 7?
?onary arterial ?ow (ml./min)	30 5 ±5 9	?8 6 ±6.2	?8 1 ±6 3	27 6 ±5 8	8? ±6 3	8 1 ±6 3	?6 9 ±5 6	23? ±5 5	?3 8 ±5 0	?0 8 ±5 0	21 0 ±5 6	10 8 ±1 5	11 1 ±1 4
?onary vascular ?sistance (10 ?ynes cm sec)	3 65 ±0 69	4 48 ±1 0?	4 ?1 ±0 92	4 6 ±0 8?	4 27 ±0 85	4 31 ±0 86	4 51 ±0 91	5 ?3 ±1 ?3	5 ?9 ±1 13	5 38 ±1 ?2	6 06 ±1 36	3 93 ±0 0	4 71 ±0 94

< 0 05

< 0.001

usion at a rate of 2 0 µg per kilogram per nute until the appearance of persistent ifocal or multifocal ventricular tachycardia ie ouabain infusion was then discontinued and imediately after spontaneous conversion to gular sinus rhythm His bundle electrograms id standard ECG s were recorded Ajmaline was ien given in the same dosage as described above wenty minutes after drug administration mea urements were repeated

C Effects on ventricular automaticity in the ormal and digitalis intoxicated dog Right ided vagotomy was performed in the control tate and then the distal end of the sectioned ight vagus was stimulated (Grass Stimulator Iodel S4) The stimulus characteristics were 5 to 0 volts frequency of 30 per second duration of 3 nsec and a total period of stimulation of 30 econds Ventricular automaticity was evaluated by counting the number of ventricular escape beats during the stimulation period All measure ments were obtained in duplicate After control recordings were made ajmaline was given to eight dogs in the dosage schedule described above Twenty minutes after each dose vagal stimula tion was carried out to evaluate the effects of the drug on ventricular automaticity Experiments were performed with digitalis intoxication (four dogs) or without digitalis intoxication (four dogs)

An additional series of studies was carried out in conscious dogs which previously underwent cardiothoracic surgery to induce advanced heart block Dose response relationships were obtained with continuous ECG monitoring to evaluate ajmaline s effect on ventricular automaticity

D Effect on ischemic arrhythmias With a technique previously described by Harris dou ble ligation of the anterior descending coronary artery was performed in five dogs under sterile conditions The dogs were allowed to recover and were studied at 24 hours following the surgical procedure Animals were allowed to stand upright supported by a Pavlovian sling ECG s were moni tored continuously during a 1 hour control state and following administration of increasing intra

results were obtained from integrating the data from the electromagnetic flowmeter for a period of 60 seconds However the instantaneous flow was also recorded to correlate and assess factors that affect phasic blood flow and to insure that the computer was not integrating spurious results Subsequent increases in ajmaline dose was administered only after a minimum of 20 minutes or when the recorded values returned to control Statistical comparison of these data was obtained by an analysis of the mean percentage change from control values by paired Student s t test

B Conscious dogs With the use of a previously described technique,[13] polyvinyl chloride catheters were implanted for chronic use so that the following pressures could be recorded central aortic right ventricular, pulmonary artery and right atrial After an appropriate training period dogs were able to maintain the upright position supported by a Pavlovian sling for periods of up to 4 hours without any significant change in the hemodynamic measurements and/or heart rate Studies were performed with this preparation in five dogs After controlled recordings were obtained in duplicate a minimum of 5 minutes apart, ajmaline was administered as an intravenous bolus into the right atrium in increasing doses of 0 25 0 5 1 0 2 0 and 4 0 mg per kilogram Recordings were made of the various pressures 5 minutes after injection After return to baseline levels additional doses were given as outlined above Cardiac outputs were also obtained during each drug administration sequence with the indicator dilution technique (indocyanine green)

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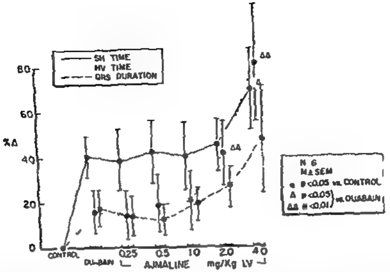

Fig 4 The effect of intravenous administration of ajmaline on atrial ventricular conduction following digitalis intoxication The horizontal axis shows ouabain dose and the increasing doses of ajmaline administered intravenously The vertical axis shows the percentage change from control. Three variables are measured as shown in the legends (see text)

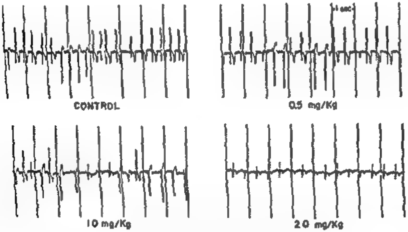

Fig 5 ECG records obtained from a typical experiment in a dog previously subjected to coronary ligation The control panel of this figure shows a recording illustrating frequent ventricular extrasystoles and short runs of ventricular tachycardia The subsequent record obtained following 0 5 and 1 0 mg per kilogram show a decrease in the frequency of ventricular extrasystoles. However following the 2 0 mg per kilogram dose of ajmaline sinus rhythm was restored

0 40 and 8 0 mg per kilogram whereas mean coronary vascular resistance increased at the first two dose levels The mean stroke index and mean systemic vascular resistance were unaffected throughout the dose range used

B Conscious dogs The hemodynamic effect of increasing doses of intravenous ajmaline was tested in five conscious dogs (Table II) Ajmaline produced an increase in cardiac rate which achieved statistical significance only at the 4 0 mg per kilogram dose The arterial pressure also was noted to rise but achieved statistical significance only at the 4 0 mg per kilogram dose No significant changes in total peripheral resistance were observed Stroke volume decreased in all dosage ranges used Ajmaline had variable effects

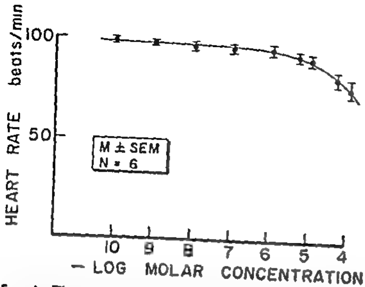

Fig 1 The effect of increasing molar concentrations of ajmaline on the heart rate of isolated cat right atria The horizontal axis shows the heart rate in beats per minute No statistically significant change in rate from control was noted throughout the entire range of drug concentrations utilized

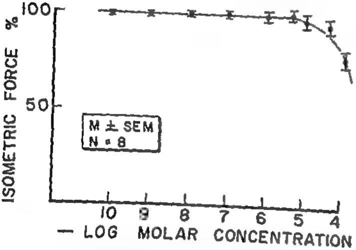

Fig 2 The effect of increasing molar concentration of ajmaline on peak isometric force of isolated cat papillary muscle The horizontal axis shows the molar concentrations of ajmaline and the vertical axis shows the isometric force expressed as a per cent of control Note that although exposure to 1 × 10 M ajmaline produced a decrease in peak isometric force this value did not achieve statistical significance

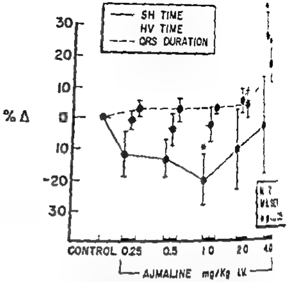

Fig 3 The effect of intravenous administration of ajmaline on atrial ventricular conduction The horizontal axis shows the doses of ajmaline used and the vertical axis shows the percentage change from control Three variables are shown as illustrated in the legend (see text)

venous doses of ajmaline from 0 5 to 2 0 mg per kilogram

E Electrophysiologic studies in conscious dogs With previously described techniques electrograms were recorded from the following sites in the conscious dog right atrium near the sinus node, left atrial appendage His bundle right ventricular free wall and left ventricular free wall Dogs were studied in the conscious state in the standing position while being supported by a Pavlovian sling Electrograms were displayed on a photographic oscilloscopic recorder (Electronics for Medicine Model DR 16) with band pass filters set at 40 to 500 Hz Conduction times were measured from the initial portion of the high frequency deflection The conduction times were assessed in the control state and following administration of increasing doses of intravenous ajmaline from 0 5 to 2 0 mg per kilogram

Statistical methods All data were analyzed by paired t testing expressed as mean values ± the standard error of the mean

Results

I Hemodynamic studies

A Anesthetized dogs The effect of increasing doses of ajmaline on hemodynamics was evaluated in seven anesthetized open chest dogs (Table I) At doses of 1 0 mg per kilogram or less, no significant hemodynamic changes were observed

The mean heart rate was not significantly altered until a dose of 8 0 mg per kilogram was given when a statistically significant decrease was seen together with mean arterial blood pressure mean LV max dP/dt mean stroke work index and mean cardiac index At a dose of 4 0 mg per kilogram mean left ventricular end diastolic pressure increased significantly and this increase was also found at the maximal dose level The mean left anterior descending coronary arterial flow diminished significantly at doses of

iterval was shortened by ajmaline adminis n but reached statistical significance only at e of 1 0 mg per kilogram

Effects on digitalis intoxication The effect creasing doses of intravenous ajmaline on ac conduction was tested in six dogs who pretreated with toxic doses of ouabain (Fig Ouabain significantly prolonged the SH val with prolongation of HV and QRS dura also observed Administration of increasing of ajmaline intravenously produced no ner significant change in QRS duration when pared to data following ouabain However interval and SH interval were significantly onged at doses of 2 0 and 4 0 mg respec ly

Ventricular automaticity The effect of easing intravenous doses of ajmaline on tricular automaticity was assessed in eight s No significant change in ventricular auto aticity was observed throughout the experi its performed both in the control state and owing digitalis intoxication However sinus ape beats were observed during intense vagal nulation at ajmaline doses equal to or greater in 2 0 mg per kilogram (Table III *A*) Studies were also performed in four conscious s with surgically induced AV block These idies demonstrated no significant changes in rate of the ventricular escape pacemaker at naline doses from 0 5 to 3 0 mg per kilogram ravenously (Table III *B*)

D Ischemic arrhythmias The effect of increas doses of intravenous ajmaline was tested in e dogs 24 hours following coronary ligation ow doses of ajmaline produced no significant fect on the frequency of ventricular arrhyth ias However doses of 2 0 mg per kilogram variably produced dramatic decreases in the equency of ventricular arrhythmias or elimi ated the arrhythmia completely with restora on of sinus rhythm (Fig 5)

E Electrophysiologic studies in conscious dogs The effect of increasing doses of intra enously administered ajmaline were tested in ive conscious animals (Fig 6) No significant hange in the AH interval was noted throughout he experimental period However there was a ignificant increase both in the HV interval and heart rate at doses equal to or greater than 1 0 mg per kilogram

Table III Ventricular automaticity

Control	After ouabain	*Ajmaline (mg / kg I V)*			
		0 5	*0 5*	*1 0*	*2 0*
***A** Anesthetized dogs*†					
8 3 ±4 9 N = 4		6 8 ±2 4	1 3 ±1 3	9 0 ±2 7	12 ? ±3 4
9 5 ±5 3 N = 4	12 5 ±6 5	10 7 ±9 2	9 8 ±6 4	10 0 ±6 3	14 2 ±4 9

Control	*Ajmaline (mg / kg I V)*			
	0 5	*1 0*	*2 0*	*3 0*
***B** Conscious dogs*‡				
45 ±7 2 N = 4	46 ±5 8	48 ±6 4	4? ±6 8	46 ±5 7

Data obtained in studies on the effects of ajmaline on ventricular automaticity All numbers are expressed as the means and their standard errors. No experimental values were statistically different from control

†Ventricular escape beats during 30 seconds of vagal stimulation

‡Rate of ventricular escape pacemaker

Discussion

Present information available from electrophysiologic studies suggests that arrhythmia development in man appears to be related to one of two basic mechanisms (1) enhanced automaticity and (2) re entry Therapy directed toward rhythm disturbances due to enhanced automaticity would require that an antiarrhythmic drug have profound suppressant effect on Phase IV depolarization In contrast therapy directed toward re entry arrhythmias may be successful due to either depression or enhancement of conduction velocity in the re entrant loop

Our observations concerned with the effect of ajmaline on ventricular automaticity would suggest that this drug does not in fact significantly alter this variable It indeed would be expected that release of neurotransmitting agents secondary to parenteral administration of this drug might result in enhancement of Phase IV depolarization in areas with automatic firing

Our studies also evaluated the effects of ajmaline on sinus node automaticity These series of experiments demonstrated a biphasic response a negative chronotropic effect in isolated atria and in the anesthetized animal and a positive

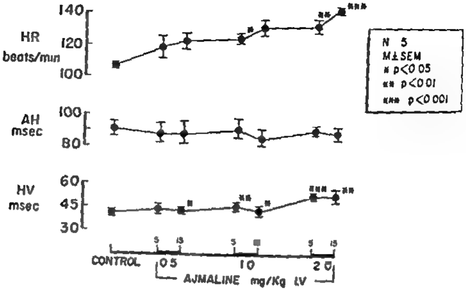

Fig 6 Electrophysiologic studies in the conscious dog On the horizontal axis the dosage of ajmaline used is shown both at 5 and 15 minutes following the dose On the vertical axis are shown those variables measured (see text)

Table II Hemodynamics (conscious dog)

	Control	Per cent change				
		Ajmaline (mg/kg)				
		0 25	0 5	1 0	3 0	4 0
Heart rate (beats/min)	73 8 ±6 1	−4 1 ±[illegible]	12 5 ±15 5	16 8 ±11 0	23 4 ±9 6	34 1† ±9 8
Cardiac output (L /min)	4 02 ±0 39	−18 9 ±6 8	−6 0 ±14 4	−5 9 ±10 1	0 3 ±14 5	3 0 ±14 6
Blood pressure (mm Hg)	126/78 ±[illegible]/4 1	−0 3/−2 2 ±2 1/3 0	4 7/1 3 ±3 [illegible]/4 6	6 5/8 6 ±2 5/4 8	5 0/7 2 ±3 7/6 [illegible]	[illegible]
Total peripheral resistance (mm Hg min /L)	24 2 ±1 9	2[illegible] 5 ±11 0	18 6 ±15 4	21 8 ±8 6	13 3 ±12 [illegible]	5 9 ±14 6
Stroke volume (mL)	5[illegible] 2 ±[illegible]3	−1[illegible] 6 ±4 8	−16 2* ±8 2	−21 6 ±5 6	−17 9 ±10 8	−31 9 ±9 5

p < 0 05
†p < 0 01

on cardiac output which achieved significance only at the 0 25 mg per kilogram dose reflecting a decrease in stroke volume but no significant change in heart rate

C In vitro studies HEART RATE The effect of increasing molar concentrations of ajmaline on the heart rate of isolated cat right atria was tested in six experiments Although ajmaline ≥ 5 × 10⁻⁵M produced negative chronotropic effects, no values achieved statistical significance (Fig 1)

ISOMETRIC FORCE The effect of increasing molar concentrations of ajmaline on the isometric force of isolated cat papillary muscles was tested in eight experiments (Fig 2) Although concentrations greater than or equal to 5 × 10⁻⁵ ajmaline decreased peak isometric force no values achieved statistical significance Most prominent depression of isometric force was noted at concentration of 1 × 10⁻⁴M

II Electrophysiologic studies

A Effects on AV conduction The effect of increasing doses of intravenous ajmaline on cardiac conduction was tested in seven dogs (Fig 3) The HV interval and QRS duration were statistically significantly prolonged only at concentration of 4 0 mg per kilogram lower doses produced no significant effect In contrast,

not affected by ajmaline doses within the
peutic range In higher concentrations a
ed reduction in coronary flow is seen This
tion in flow may reflect coronary vasocon
ion since blood pressure and cardiac con
ility remain intact at doses of 2 and 4 mg
ilogram At a dose of 8 mg per kilogram
ased coronary flow [illegible] associated with
ased blood pressure and diminished contrac

conclusion, ajmaline a derivative of
uolfia serpentina has been demonstrated to
highly effective agent for the treatment of
ythmias in man Our present experimental
ence suggests that its main mechanism of
on is due to depression of intraventricular
duction In addition it appears to be effica
s for the treatment of arrhythmias due to
tricular ischemia but it has limited benefit in
treatment of digitalis induced AV conduction
ay Finally it produces minimal hemodynamic
nges at doses below 2 0 mg per kilogram but
igher doses detrimental hemodynamic effects
noted

mmary

Ajmaline a rauwolfia derivative has been
und to possess potent antiarrhythmic effects
e present study has been designed to define the
rdiovascular effects of this drug Hemodynamic
idies performed in anesthetized and conscious
[illegible] demonstrated no significant changes in
asured hemodynamic parameters at doses
ual to or less than 2 mg per kilogram Studies
isolated papillary muscle demonstrated no
gative inotropic effects until concentrations of
× 10 Disparate results were obtained with
gard to heart rate reflecting the state of
itonomic tone Electrophysiologic studies in
oth anesthetized and conscious dogs demon
rated a significant depression of intraventric
lar conduction with no significant effect on AV
odal conduction ventricular automaticity was
ot affected Ajmaline did not alter digitalis
iduced AV nodal conduction prolongation
However ajmaline dramatically altered or abol
shed ventricular arrhythmias secondary to acute
schemia In conclusion these studies demon
trate that ajmaline specifically depresses intra
entricular conduction suggesting that this drug
would be particularly effective in the treatment
of re entrant ventricular arrhythmias

The authors gratefully acknowledge the technical assistance of Avile McCullen and Leonard Chuck and the editorial assistance of Mrs. Betty Garrigues.

REFERENCES

1 Siddiqui, S and Siddiqui, R. H The alkaloids of *Rauwolfia serpentina* benth Part I J Indian Chem Soc 9 539 1932
2. Arora R. B and Madan, [illegible] R Antiarrhythmics VI Ajmaline and serpentine in [illegible]perimental cardiac arrhythmias, J Pharmacol. Exp Ther 117 62 1956.
3. Dick, H L. H., and McCawley E. L. Clinical pharmacologic observations in the effects of ajmaline in chronic atrial fibrillation Clin Pharmacol. Ther 4 315 1963
4 Slama R Foucault J and Bouvrain Y Le traitement d urgence des troubles du rhythme cardiac par l ajmaline intraveineuse Presse Med. 71 2250 1963
5 Bazika V Lang T W Pappelbaum [illegible] et al Ajmaline a Rauwolfia alkaloid for the treatment of digitoxic arrhythmias, Am J Cardiol. 17 227 1966
6 Pistolese M and Catalano V Trattamento dei ritmi ectopici con ajmalina per via endorenosa Minerva Med. 57 1300 1966
7 Lampertico M Valutazione della terapia ajmalinica in 187 pazient Minerva Med 62 1197 1971
8 Puesch P Latour H Hertault J et al L ajmaline injectable dans les tachycardies paroxystiques et le syndrome W P W Comparaison avec le procainamide Arch Mal Coeur 57 897 1964
9 Soler Soler J Casellas Bernat A and Trilla Sanchez, E Accion de la ajmalina en el sindrome de Wolff Parkinson White Utilidad diagnostica Arch Inst Cardiol Mex 36 [illegible] 1966
[illegible] Tronconi L. L impiego dell ajmalina per via venosa e della procaineamide nel trattamento della sindrome di Wolff Parkinson White Minerva Cardioangiol 14 728 1966
11 Wellens H J J and Durrer D Effect of procaine amide quinidine and ajmaline in the Wolff Parkinson White syndrome Circulation 50 114 1974
12. Irving, D W and Corday [illegible] Effect of the cardiac arrhythmias on renal and mesenteric circulations Am J Cardiol. 8 32 1961
13 Laks M M Callis, G and Swan H J C Hemodynamic effects of low doses of norepinephrine in the conscious dog Am J Physiol 220 171 1971
[illegible] Parmley W W and Braunwald E Comparative myocardial depressant and antiarrhythmic properties of *d* propranolol *dl* propranolol and quinidine J Pharmacol Exp Ther 158 11 1967
15 Harris A S Delayed development of ventricular ectopic rhythms following experimental coronary occlusion, Circulation 1 1318, 1950
16 Stuckey J H Hoffman [illegible] F Bagdonas, A A. et al. Direct recordings from chronically implanted electrodes on the specialized conducting system of the heart Proc Soc Exp Biol Med 106 90 1961
17 Cranefield P F Wit A L and Hoffman B F Genesis of cardiac arrhythmias Circulation 47 190 1973
18. Bigger J T Jr Arrhythmias and antiarrhythmic drugs, Adv Intern Med 18 251 1972.
19 Goodman L S and Gilman, A. The pharmacological basis of therapeutics, ed. 4 New York 1970 The Macmillan Company
20 Brooks, C McC and Lu H H The sinoatrial pacemaker of the heart Springfield, Ill 1972, Charles C Thomas, Publisher
21 Solberg, L Ten Eick R and Singer [illegible] Electrophysio-

chronotropic effect in the conscious dog The dual effect observed can, in part, be explained by the markedly altered (or absent) autonomic neural and central neural control The positive chronotropic effect observed in the conscious animal may be best explained by the dominance of local (atrial) release of catecholamines following intravenous ajmaline administration[19] No reflex changes would be expected to be in effect as systemic pressure was unchanged or elevated

Ajmaline's different effects on sinus and ventricular automaticity may be explained by recent data which suggest that the development of Phase IV depolarization in these two areas may be due to different electrophysiologic mechanisms[20] Therefore, it is not inconceivable that a drug may have a significantly different effect in these two tissue types

In contrast to our observations concerning ventricular automaticity, our experimental results in both anesthetized and in conscious dogs confirm that ajmaline significantly depresses intraventricular conduction These observations would support the concept that ajmaline's basic mechanism of antiarrhythmic action appears to be depression of conduction with possible elimination of reentrant arrhythmias

A major concern of clinicians in the last several years has been the treatment of arrhythmias due to ischemic heart disease The mechanism responsible for arrhythmias seen in ischemic myocardium has recently been the subject of intensive study Available evidence to date suggests that early in the time course of ischemia enhanced automaticity may occur even in ventricular myocardium and, therefore be responsible for ventricular arrhythmias, continued exposure to ischemia produces arrhythmias due to re entry[21,23] Nevertheless, the present therapy available for arrhythmias secondary to ischemia appears to be, on occasion unsatisfactory Our experimental results have identified the fact that in the setting of acute ischemia ajmaline at a dose of 2 mg per kilogram, appears to be highly effective for the treatment of significant ventricular arrhythmias

Arrhythmias secondary to digitalis intoxication are frequently observed in the hospital setting[24,25] Presently available antiarrhythmic drugs are generally satisfactory for the treatment of digitalis induced ventricular arrhythmias but have limited effectiveness in terms of treatment of digitalis induced depressed AV conduction[18,4] Our present experimental data do not suggest that ajmaline would have any potential benefit for the treatment of depressed AV conduction secondary to digitalis overdosage

Of additional significance is the hemodynamic effects which are associated with antiarrhythmic drug adminsitration Detrimental hemodynamic effects may be observed with all antiarrhythmic agents, but appear to be most commonly ot with the use of procaine amide, quinidine, propranolol[19] It would, therefore appear essential to have an antiarrhythmic agent which possess minimal negative inotropic effects.

Our data available in the conscious dog demonstrated no significant changes in measured hemodynamic parameters except for an elevation in arterial pressure and heart rate, seen only following high doses (4 mg per kilogram) which are probably toxic Our studies in the anesthetized open chest animal with low dosage ajmaline demonstrated a similar lack of hemodynamic effects However, when used in high dosage excess of 4 mg per kilogram, ajmaline produced some detrimental hemodynamic effects which may be of clinical significance in that mean left ventricular end diastolic pressure rose as did mean coronary vascular resistance

The hypotensive reactions seen at very high doses of ajmaline (8 mg per kilogram) are not caused by a vasodilating effect but may be attributed to reduced cardiovascular performance since mean systemic vascular resistance was not significantly altered throughout the dosage used, mean stroke work index fell, and mean left ventricular end diastolic pressure rose still further

The reported effect of ajmaline on cardiac contractility is variable Kleinsorge[8] has reported in his clinical study that ajmaline has positive inotropic effects In other experimental studies it was shown that ajmaline possesses negative inotropic effects[27,8] Our data show that with therapeutic doses ventricular contractility was not affected since max LV dP/dt was unchanged until a dose of 8 mg per kilogram and left ventricular pressure was elevated only at doses of 4 and 8 mg per kilogram Furthermore, studies in isolated papillary muscle showed no significant reduction in peak isometric force with exposure up to 1×10^{-4}M

Left anterior descending coronary blood fl

·raventrıcular trıfascıcular block verıfıed by ͅ bundle electrocardıography

ıl E Bloch Thomsen
ıt Sterndorff
ınıng Gøtzsche
hus Denmark

ra\entrıcular trıfascıcular block (ITB) has ıı introduced and classıfied by Lepeschkın l by Rosenbaum and associates The ıdrome ımplies ımpaıred conductıon ın the ee maın termınal fascıcles of the ıntraventrıcu conductıon system at the same tıme

The concept of the anatomıc structure of the ra\entrıcular conductıon system ın three fascı s has recentl\ been challenged by several thors as beıng an o\ersımplıficatıon The ıtence of A V conductıon dısturbances occur ıg ın three separate pathways would lend pport to the three fascıcle concept but has untıl w been reported ın few cases Any further o\ed cases of ITB would therefore be of funda ental ınterest

The present report deals wıth a patıent ın hom ITB manıfested ıtself b\ the occurrence of rıght bundle branch block (RBBB) wıth ternatıng patterns of left anterıor hemıblock AH) left posterıor hemıblock (LPH) and rade 2 A V block studıed b\ Hıs bundle recor ıngs

·ase report

The patıent a / \ear old woman had dıphtherıa at the age l 15 but apart from that she had been ın good health In 1961 t the age of 64 she began to feel d\spnea and oppres ıon at tertıon She was then hospıtalızed elsewhere and was found) ha\e mıld left sıded heart faılure She was treated wıth ıgıtalıs and dıuretıcs but stopped the treatment after nausea ın electrocardıogram (ECG) obtaıned durıng dıgıtalıs treatment showed RBBB wıth LPH and probable Cohn effect (Fıg. 1 *a*) In 197? when the patıent was 75 years *old the ECG* showed RBBB wıth LAH and a slıght prolongatıon of the P R ınterval (Fıg. 1 *b*)

She was admıtted to our department on Sept. 26, 19 4 At that tıme she had suffered from sudden spell of dızzıness and weakness for about 3 months. Other symptoms were nocturnal d\spnea and attacks of angına pectorıs at exercıse but never at rest Now the ECG showed (Fıg 2) a Grade 2 4 3 A V blo k wıth RBBB and alternatıng LPH and LAH after the conducted P waves. There was no sıgn of m\ocardıal ınfarctıon After Hıs bundle recordıngs a demand ventrıcular pacemaker was ımplanted.

Electrophysıologıcal studıes Hıs bundle electrograms were obtaıned wıth conventıonal technıque and showed (Fıg. 3) (1) 4 3 A V block dıstal to the A V node (?) ın the three conducted beats ın each sequence there ıs a shıft between RBBB wıth LPH and RBBB wıth LAH (3) A H ıntervals at 90 msec (normal, 55 to 130) ındıcate a stable A V nodal conductıon (4) H V ınterval ıs 80 msec (normal, 30 to 55) when the ımpulse ıs conducted through the left *anterıor* fascıcle and 110 msec when conducted through the left posterıor fascıcle

Several tracıngs were avaılable durıng Hıs bundle recor dıngs, all showıng a Grade 2 A V block but wıth varyıng A V ratıos (2 1 3 2, and 4 3) All tracıngs show a RBBB + LPH pattern after P wa es followıng nonconducted P waves (Fıgs. 3 and 4)

Dıscussıon

Hıs bundle electrograms (HBE) confırmed that A V conductıon dısturbances were located dıstal to the A V node

Sınce RBBB ıs permanent and the P rhythm ıs constant HBE proved (1) that thıs specıal type of ITB appears when the two left fascıcles are only partıally damaged and (2) that they are damaged to a dıfferent degree as evıdenced here by the two dıfferent and prolonged conductıon tımes (80 and 110 msec)

The mechanısm of total blockıng after some P

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Recei ed for p b ıc tıo A g. 5 19 5

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logical basis of arrhythmias in infarcted ventricle Circulation 46 (Suppl II) 116 1972

22 Friedman P L Stewart J R and Wit A L Spontaneous and induced cardiac arrhythmias in subendocardial Purkinje fibers surviving intensive myocardial infarction in dogs Circ Res. 33 612 1973

23 Lazzara R El Sherif N and Scherlag B J Early and late effects of coronary artery occlusion on canine Purkinje fibers Circ Res 35 391 1974

24 Sodeman W A Current concepts Diagnosis and treatment of digitalis intoxication N Engl J Med 273 35 93 1965

25 Irons G V Jr and Orgain E S Digitalis induced arrhythmias and their management Prog Card[illegible] Dis 8 539 1966

26 Kleinsorge H Klinische Untersuchung [illegible] Wirkungsweise des Rauwolfia alkaloids Ajmalin [illegible] Herzrhythmusstorungen insbesondere der Extra[illegible] Med Klin 54 409 1959

27 Schmitt H and Schmitt H Sur la pharma[illegible] l ajmaline Arch Int Pharmacodyn 127 163, [illegible]

28 Petter H and Zipf K Ein Fluss der Extra[illegible] Kalium Konzentration auf die kontraktions[illegible] llosierten vorhofs nach Ajmalinbehandlung [illegible] Schmiedebrgs Arch Exp Pathol Pharmakol [illegible] 1962

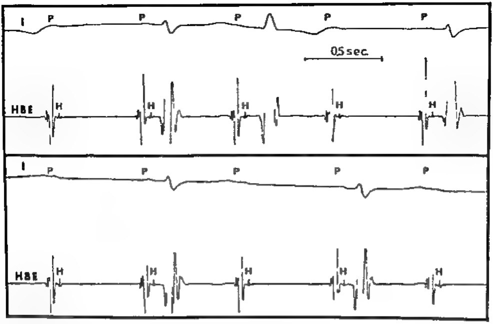

Fig 4 His bundle recordings from Sept 27 19 4 Upper tracings A 3 2 A V block distal to the A V node There is a shift between RBBB with LPH and RBBB with LAH in the conducted beats Lower tracings A ? 1 A V block distal to the A V node QRS complexes demonstrate RBBB with LPH Abbreviations, atrial rate and intervals as in Fig 3

aves is unsettled It may result from a Mobitz II mechanism in the remaining main stem of the bundle of His An explanation assuming a coincidence of refractoriness in the two fascicles of the left bundle seems less probable considering the demonstrated variability of A V ratio

A Mobitz II mechanism in but one of the left fascicles is unlikely too as the last QRS complex before a blocked beat can have either LPH or LAH configuration (Figs 3 and 4)

An explanation of the constant LPH pattern in the first conducted beat after a blocked beat is more straightforward After a blocked P wave both fascicles are likely to conduct the impulse arriving through the His bundle However since the left anterior fascicle conducts faster than the left posterior fascicle and since RBBB is permanent the QRS complex in the first conducted beat should always appear as RBBB with LPH which was actually the case (Figs 3 and 4)

Finally other mechanisms may be considered for the Grade 2 A V block e g concealed conduction antegrade or retrograde in the two left sided fascicles or blocking of the impulse in the distal gate"

Summary

A patient with the combination of right bundle branch block and intermittent left anterior and left posterior hemiblock is presented His bundle recordings proved that this type of intraventricular conduction defect appeared when the two left fascicles were damaged partially and to a varying degree The recordings also revealed a Grade 2 A V block distal to the A V node The mechanism is discussed

REFERENCES

1 Lepeschkin E The electrocardiographic diagnosis of bilateral bundle branch block in relation to heart block Prog Cardiovasc Dis 6 445 1964

2 Rosenbaum M B Elizari M V Lazzari J O Nau J G Levi R J and Halpern M S Intraventricular trifascicular blocks. The syndrome of right bundle branch block with intermittent left anterior and posterior hemiblock Am Heart J 78 306 1969

3 Rosenbaum M B Elizari M V Lazzari, J O Nau J G Levi, R J and Halpern M S Intraventricular trifascicular blocks. Review of the literature and classification Am Heart J 78 450 1969

4 Uhley H N Some controversy regarding the peripheral distribution of the conduction system Am J Cardiol 30 919 19 2

5 Demoulin J C and Kulbertus, H E Left hemiblocks revisited from the histopathological viewpoint Am Heart J 86 12, 19 3

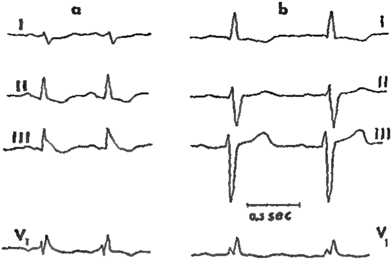

Fig 1 (*a*) ECG July 11 1961 Pattern of RBBB with LPH AQRS +110 P R interval 0 16 sec S T segments reveal digitalis effect (*b*) ECG Oct 26 1972 showing RBBB with LAH AQRS −60° P R interval 0 [illegible] sec

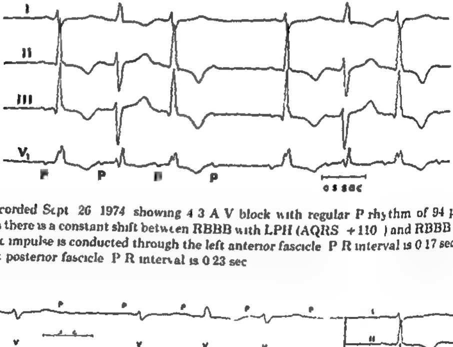

Fig 2 ECG recorded Sept 26 1974 showing 4 3 A V block with regular P rhythm of 94 per minute In the conducted beats there is a constant shift between RBBB with LPH (AQRS +110) and RBBB with LAH (ÂQRS −60) When the impulse is conducted through the left anterior fascicle P R interval is 0 17 sec When conducted through the left posterior fascicle P R interval is 0 23 sec

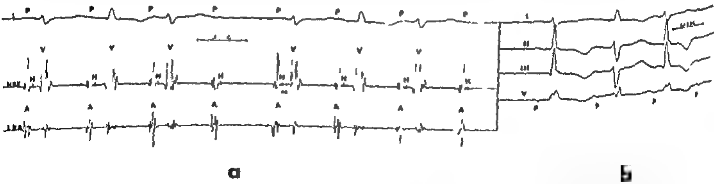

Fig 3 (*a*) His bundle recordings made Sept 27 1974 Shown are ECG Lead I (*I*) His bundle electrogram (*HBE*) and a low right atrium electrogram (*LRA*) For verification of the type of bundle branch block compare with Fig 3, *b* P waves are labeled *P* Atrial rate (*P*) is 94 per minute *A* is low atrial depolarization *H* is His potential and V is ventricular depolarization There is a 4 3 A V block distal to the A V node In the conducted beats there is a constant shift between RBBB with LPH and RBBB with LAH and the conduction times (*H V intervals*) through the His Purkinje system are through the left anterior fascicle 80 msec through the left posterior fascicle 110 msec Constant A H intervals at 90 msec (*b*) ECG made immediately after His bundle recordings showing the ECG patterns of alternately RBBB with LPH (ÂQRS +110) and RBBB with LAH (ÂQRS −60) Atrial rate is 94 per minute

ute coronary occlusion following blunt injury the chest in the absence of coronary ierosclerosis

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onpenetrating injury to the chest may cause ntusion of the heart muscle the clinical mani tations of which have been described by rious authors Cases of transmural myocar al infarction have also been reported following ich chest trauma although only rarely with igiographic documentation[9] The pathogenesis myocardial infarction in such cases and its lationship to pre existing atherosclerotic coro ary disease and to myocardial contusion remain nsettled The purpose of this communication is o report a case of acute inferoposterior myocar ial infarction with angiographically demon trated complete obstruction of the left circum lex artery but no signs of atherosclerotic disease n the other coronary arteries Observations are nade on the etiology of myocardial infarction ollowing blunt chest trauma in the light of the indings in this case

Case report

A 35 year old man was admitted to the hospital an hour after he was hit by a fist in the sternal area of his chest. He was free of symptoms for a period of 30 minutes and then began to experience intense chest pain which radiated to both shoulders and was accompanied by palpitation shortness of breath, profuse sweating and dizziness, all of which lasted for a few hours. The patient had never been ill before and did not have a family history of heart disease hyperlipidemia hypertension or diabetes mellitus.

On admission the patient appeared pale the blood pressure was 1.0/90 mm Hg the pulse was regular at 84 per minutes. There were no external signs of injury to the chest and no local tenderness was elicited The heart sounds were normal and no murmur was detected The lungs were clear and there was no evidence of heart failure A chest x ray was normal and revealed no fractures of the thoracic cage Serum electrolyte values were normal The electrocardiogram (ECG) on admission showed slight elevation of the ST segment in Leads II III, aV V = V and T wave inversion in aV and V = V_r. On repeated ECG recordings signs of transmural inferior and true posterior wall infarction appeared with injury extending to the lateral wall (Fig 1)

A marked leukocytosis and rise in the lactic dehydrogenase (LDH) and glutamic oxalacetic transaminase (GOT) levels occurred in the first few days, LDH reaching its maximal level of 1,250 U on the third day LDH isoenzyme study showed a rise in fraction LDH and LDH_r. Fasting glucose cholesterol and triglycerides were normal.

The clinical course was uncomplicated except for occasional premature ventricular contractions during the first few hours and transient pericarditis on the fourth day

The patient was kept on complete bed rest for 11 days, following which he was gradually mobilized he was discharged on the seventeenth day Throughout his hospitali zation the patient had shown no evidence of congestive heart failure and repeated chest x rays were normal.

During subsequent months the patient gradually developed dyspnea and intense chest pain appearing mainly during effort, but also occurring with no relation to physical activity Because of this the patient was readmitted to the hospital for selective coronary angiography This examination performed by the Judkins technique showed a complete occlusion of the left circumflex coronary artery (Figs. 2 and 3) The obstruc tion was 2 cm distal to the origin of the artery and no runoff was visualized. All other coronary vessels were normal (Fig 4) Left ventriculogram revealed a small area of akinesis on the inferior wall of the left ventricle

During follow up of 9 months the patient continued to have typical anginal pains not responsive to therapy ECG exami nation revealed no dynamic changes (Fig 5)

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This tudy was pported by the M rto Steinbe g P rpetual End w ment M mori l F d

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6 Fleischmann D Effert S and Bleifeld W Trifaszikulärer Herzblock Klin Wochenschr 51 541 1973
7 Scherlag B J Lau S H Helfant R H Berkowitz W D Stein E and Damato A N Catheter technique for recording His bundle activity in man Circulation 39 13 1969
8 Hecht H H Kossmann C E Childers R W Langendorf R Lev M Rosen K M Pruitt R D Truex R C Uhley H N and Watt T B Atrioventricular and intraventricular conduction Revised nomenclature and concepts Am J Cardiol 31 232 1973
9 Ali N Wichramasekaran R Fahdul H and Bashir Wenckebach periods in posterior inferior division of bundle Chest 63 949 1973
10 Myerburg R J., Stewart J W and Hoffman B F Electrophysiological properties of the canine peripheral A V conducting system Circ Res 26 361 1970

Fig 2 Left coronary artery right anterior oblique

Fig 3 Left coronary artery left anterior oblique

flattening of inversion of T waves and ST segment deviation Experimental work on exposed dogs hearts and on intact dogs showed that the basic histopathologic changes in the myocardium following blunt injury were fragmentation of myocardial fibers hemorrhages and edema Damage to the pericardium and the pericardial vessels with a variable degree of hemopericardium was also frequently seen

In most of the cases of acute coronary artery occlusion associated with blunt chest injury preexisting atherosclerotic coronary artery disease has been described [3] These authors therefore assumed that in such cases pre existing coronary atherosclerosis is always present and the blunt chest injury dislodges an atheromatous plaque thus obstructing the vessel. Even in the youngest victim of blunt trauma a 10 year old boy who suffered a fatal blow to the chest while boxing atheromatous changes in the left descending coronary artery were described Our case demonstrates however that coronary disease need not always be present in such cases since all coronary arteries visualized were free from any stigma of atherosclerosis Such observation certainly bears important medicolegal implications. Moreover our case seems to support the theory that myocardial infarction due to blunt

Fig 4 Right coronary artery left anterior oblique

trauma is the result of injury to coronary vessels rather than to contusion of the heart muscle The mechanism of coronary artery occlusion in this type of injury is still obscure but it is possible that a normal coronary artery may be occluded by either a tear of the intima and/or a subintimal

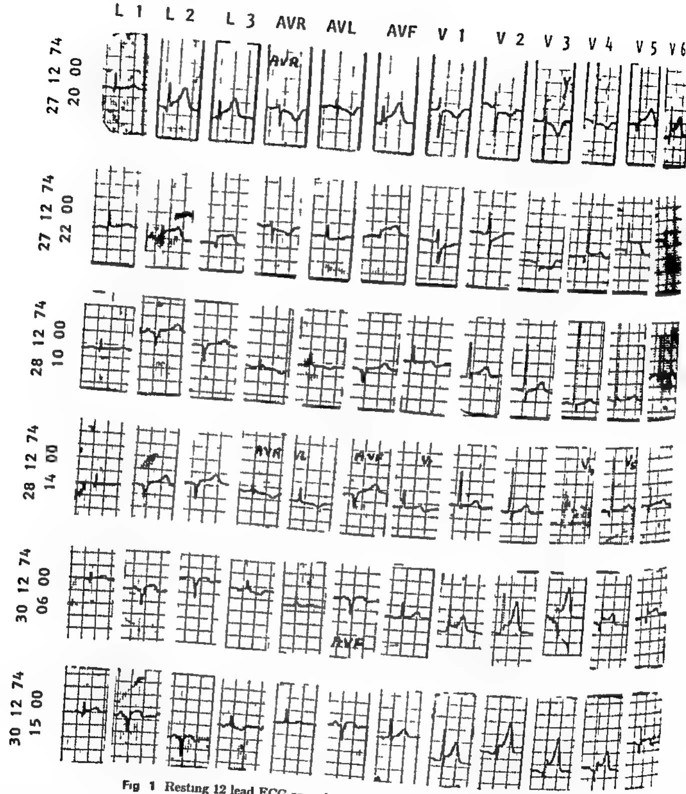

Fig 1 Resting 12 lead ECG recording during first days of hospitalization

Discussion

Although early investigators felt that the evidence for traumatic injury to the myocardium is far from conclusive, most authorities today agree that injury to the chest may induce myocardial damage [10] A wide variety of clinical manifestations can be evoked by nonpenetrating trauma to the chest of which the most dramatic are rupture of the myocardium tear of valvular cusps or of chordae tendineae and bleeding from pericardial or coronary vessels [11]

Myocardial contusion frequently occurs in road accidents after steering wheel injury Watson and Bartholomae[12] published a series of 42 patients who sustained blunt chest injury of whom 17 (38 per cent) showed ECG changes consisting of

rosby V G Coronary artery occlusion resulting from blunt trauma J A M A 230 1308 1974
riedberg, C K Diseases of the heart ed 3 Philadelphia, 1966, W B Saunders Company pp 1697 1706
armley L. F., Manion W C and Mattingly T W Nonpenetrating traumatic injury of the heart Circulation 18 371 1958.
Watson, J H and Bartholomae W M Cardiac injury due to nonpenetrating chest trauma Ann Intern Med. 52 871 1960
Moritz, A. R and Atkins, J P Cardiac contusion An experimental and pathologic study Arch Pathol 25 445 1938

14 Beckman D L., and Friedman B A. Mechanics of cardiothoracic injury in primates, J Trauma 12 620 1972.

15 Levy H Traumatic coronary thrombosis with myocardial infarction Arch. Intern Med 84 261 1949

16 Jokl E and Greenstein J Fatal coronary sclerosis in a boy of 10 years Lancet 2 659 1944

17 Arenberg H Traumatic heart disease A clinical study of 250 cases of nonpenetrating chest injuries and their relation to cardiac disability Ann Intern Med. 19 326 1943

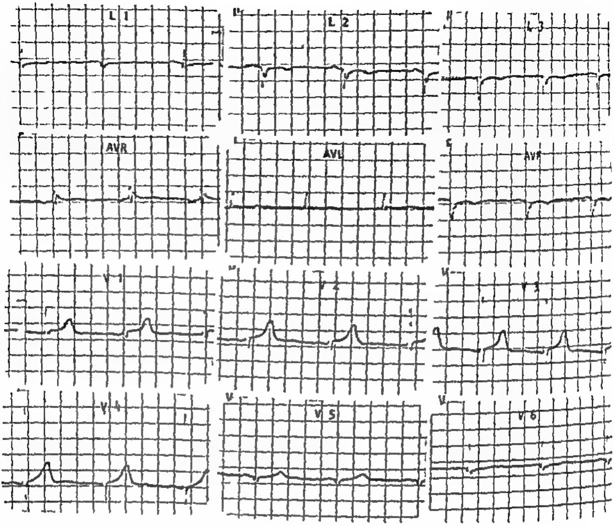

Fig 5 Resting ECG 9 months after the infarction

hemorrhage resulting in subsequent thrombosis

Arenberg[11] pointed out that cardiac disability may follow myocardial contusion Most of the 28 patients he described were in their fifth and sixth decades In our relatively young patient crippling anginal pain started immediately after his return to normal life Unfortunately the lack of "runoff" in the occluded circumflex artery prevents any possibility of surgery at present

Summary

A 35 year old man suffered transmural diaphragmatic wall infarction immediately after receiving a nonpenetrating trauma to his chest During subsequent months crippling angina pectoris developed and coronary arteriography was performed A complete obstruction of the left circumflex coronary artery was demonstrated 2 cm distal to its origin In contrast to most cases previously published, in this case no signs of atherosclerosis were observed in the other coronary arteries It must be assumed, therefore that blunt trauma can induce complete coronary occlusion with infarction even in subjects with normal coronary arteries

REFERENCES

1 Warburg E Myocardial and pericardial lesions due to nonpenetrating injury Br Heart J 2 271 1940
2 Kissane R W Traumatic heart disease—nonpenetrating injuries Circulation 6 421 1952
3 Demuth W E and Zinsser H F Myocardial contusion Arch Intern Med 155 434 1965
4 Demuth W Jr Baue E and Odom A Contusion of the heart Trauma 7 443 1967
5 Lehmus H J Sundquist A B and Giddings, L Coronary thrombosis with myocardial infarction secondary to nonpenetrating injury of the chest AM HEART J 47 470 1954
6 Borodkin H D and Franklin O Myocardial trauma produced by nonpenetrating chest injury AM HEART J 53 795 1957
7 Harthorne J W Kantrowitz P A Dinsmore R and Sanders A Traumatic myocardial infarction report of a case with normal coronary angiogram, Ann Intern Med 66 341 1967
8 Jones L Transmural myocardial necrosis after nonpenetrating cardiac trauma Am J Cardiol 26 419 19
9 Stern T Wolf R Reichart B Harrington O B

Fig 2 Esophagram in frontal (*A*) and lateral (*B*) views

rmal limits Cultures of urine and blood were erile Arterial blood gases (room air) were pH 3? Pco₂ 25 mm Hg and Po 46 mm. Hg The terial blood gases were repeated following dministration of oxygen at a flow rate of 15 L r minute for ½ hour The values obtained were H 7 43 Pco_2 25 mm Hg and Po_2 82 mm Hg

The electrocardiogram (ECG) demonstrated a RS axis in the frontal plane of +60 degrees A eep S in Lead V_1 and inverted T wave in Lead V ggested left ventricular hypertrophy No Q aves were evident in the precordial leads (Fig 1) Dr Amplatz will comment on the thoracic roent enograms

DR KURT AMPLATZ The thoracic roentgeno gram with barium in the esophagus shows gener alized moderate cardiomegaly with increased ascularity There is some thickening of the pleura of the right lung suggesting the possibility of transpleural collateral circulation Indenta tions of the proximal barium filled esophagus suggest bronchial collateral arteries or less likely an aberrant right subclavian artery (Fig 2) Were additional noninvasive studies performed?

DR. STONE An echocardiogram was performed The right ventricular chamber appeared small There was a moderate degree of thickening of both the ventricular septum and the right ventricular anterior free wall Both A V valves were identified in their usual locations A single great vessel arose from the heart in a relatively anterior position The vessel appeared to override the ventricular septum The semilunar valve of this vessel appeared atypical Multiple valve echoes were recorded from within the vessel and the cusps closed in an eccentric fashion Continu ity between the mitral valve and great vessels appeared to be present The left atrium was moderately enlarged Dr Lucas will you discuss the differential diagnosis please?

DR. RUSSELL V LUCAS JR This 5-day old infant was moderately cyanotic and in stable clinical condition The x ray revealed cardiomeg aly and definite increase in pulmonary blood flow These findings suggested one of the admixture lesions i e total anomalous pulmonary venous connection single atrium single ventricle trun cus arteriosus or complete transposition of the great vessels In addition the A V valve atresias belong with this category of lesions Auscultation did not support a diagnosis of total anomalous pulmonary venous connection nor single atrium The normal axis in the ECG made tricuspid atresia unlikely and the adequate left ventricular voltage essentially ruled out the hypoplastic left heart syndrome

The echocardiogram was most helpful in the further differential diagnosis Two A V valves two ventricular chambers and a ventricular septum were clearly identified Moreover one

Clinical pathologic conference

Ventricular septal defect, solitary aortic trunk, and ductal origins of pulmonary arteries

Frederic M Stone, M D
Kurt Amplatz M D
Russell V Lucas Jr M D
Toyoki Fukuda M D
Jesse E Edwards, M D
Minneapolis and St Paul Minn

DR FREDERIC M STONE A 5 day old female infant was admitted to the University of Minnesota Hospitals on Aug 4 1975 for evaluation of persistent cyanosis She was the product of a term uncomplicated pregnancy of a 24 year old gravida 4 para 3 woman Delivery was precipitous and complicated by a face presentation Birth weight was 3,700 grams There were ecchymoses of the face The infant was mildly cyanotic in the immediate neonatal period and the cyanosis increased with crying or stress She fed without difficulty and exhibited no signs or symptoms of congestive heart failure The mild cyanosis persisted and at 72 hours of age generalized icterus was observed An older female sibling had undergone corrective surgery for tetralogy of Fallot at the age of 4 years and several distant cousins had congenital heart disease

Physical examination showed the infant to be mildly cyanotic while breathing room air She was icteric and had resolving ecchymoses of the face and forehead The body weight was 3 380 grams the length 51 5 cm The cardiac rate was 140 per minute and the respiratory rate was 46 per minute Simultaneous flush blood pressures were 65 mm Hg in both the left arm and left leg The lungs were clear to auscultation The first cardiac sound was single and it was followed by a loud

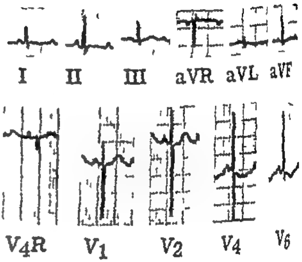

Fig 1 Electrocardiogram

systolic ejection click audible at the lower l sternal border and at the apex The seco cardiac sound was single and moderately accn tuated There was a Grade 4/6 systolic ejectio murmur with maximal intensity at the uppe right sternal border This murmur was well hea over the precordium and the back No dia tolı murmur was audible Peripheral pulses were fu and of equal character in all extremities The hepatic edge was palpated 2 cm below the righ costal margin The splenic tip was palpable The remainder of the physical examination was u markable

Laboratory studies gave the following results The hemoglobin concentration was 20 5 Gm per 100 ml and the hematocrit was 62 per cent Total bilirubin was 10 mg per 100 ml An ABO antibody screen was negative The VDRL was negative Leukocyte count urinalysis and concentration of the serum electrolytes and serum protein as determined by electrophoresis were all with

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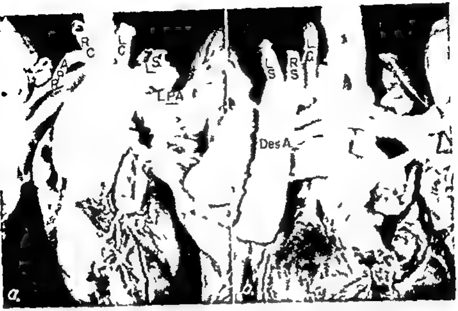

Fig 4 A Heart and lungs from in front Solitary aortic trunk arises from right ventricle The aortic arch is left sided First branch of aortic arch terminates as the right common carotid (*R C*) and distal ductal origin of right pulmonary artery (*R P.A*) Second branch of aortic arch is left common carotid artery (*L C*) Ductal origin of left pulmonary artery (*L P.A*) arise from aortic arch just proximal to left subclavian artery (*L S*) *B* Posterior view showing trachea and descending aorta (*Des A*) (Esophagus has been removed) Branches of aortic arch shown from before backward are the left common carotid (*L C*) left subclavian (*L.S*) and right subclavian (*R.S*) arteries In the natural state the right subclavian artery was directed toward the right

low quality for reproduction Resuscitative forts were continued but were unsuccessful and ie patient died in the catheterization laboratory r Lucas would you continue the discussion in ,ht of the additional findings?

DR. LUCAS The left to right atrial shunt and ie demonstration of higher pressures in the left trium than in the right were evidence that the ompliance of the left ventricle was lower than hat of the right Measurements of pressure in the eft ventricle and left ventriculography were leemed the next steps However once the cath ter was inserted into the left ventricle a series of irrhythmias occurred which were never ade quately controlled and ultimately led to the child s death

As Dr Amplatz has indicated the right ventric ulogram confirmed the presence of a small tra beculated right ventricle noted on the echocardio gram It also suggested that the aorta arose from the right ventricle and that the aortic valve was stenotic The source of blood flow to the lungs appeared to be through two vessels arising from the aortic arch one from the innominate artery to the right pulmonary artery and one from the lesser curvature of the arch leading to the left pulmonary artery

In summary the clinical and catheterization data were consistent with the origin of the aorta (or truncus) from the right ventricle obstruction of left ventricular output by a small ventricular septal defect probable stenosis of the aortic (truncal) valve and supply of the pulmonary arteries through bronchial or ductal vessels

DR STONE Dr Fukuda would you please describe the autopsy findings?

DR. TOYOKI FUKUDA Pertinent pathologic findings were related to the heart lungs and great vessels (Figs 3 and 4) The ascending aorta was enlarged and was the only artery arising from the heart A pulmonary trunk or vestige thereof could not be identified The aortic arch passed over the left main bronchus and gave branches in the following manner The first branch from the aortic arch was the usual position of an innomi nate artery This vessel terminated by branching into the right common carotid artery and an artery that proceeded toward the hilus of the right lung where it continued as the right pulmo nary artery At a distance of 7 mm from the

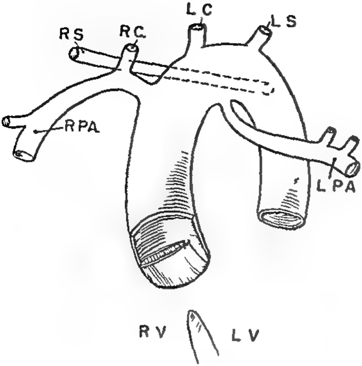

Fig 3 Diagrammatic summary of the vascular anomalies observed at autopsy

large great vessel was the only vessel detected arising from the heart The echocardiographic diagnosis of truncus arteriosus was consistent with most of the other clinical features There were several features of this case however that continued to be of concern The systolic ejection murmur heard in the aortic area was typical for aortic valvular stenosis The right ventricular dimension on echocardiography (small chamber size and thick wall) was not typical for truncus arteriosus and the characteristics of valve closure in the echocardiogram suggested abnormal function of the truncal valve We considered the possibility of truncus arteriosus with truncal valve stenosis or origin of both great vessels from the right ventricle with aortic stenosis and pulmonary atresia The ECG findings of left ventricular hypertrophy and strain raised the possibility of a flow restricting ventricular septal defect as the sole outlet from the left ventricle Our failure to establish a definitive diagnosis and the fact that at least one of the lesions might be ductus dependent were considered indications for cardiac catheterization

Dr Stone The hyperbilirubinemia was treated with phototherapy with an adequate response No signs or symptoms of congestive heart failure appeared but the infant remained persistently cyanotic During the second hospital day, further diagnostic studies were performed in the cardiac catheterization laboratory

No presedation was employed The catheter was introduced into the right saphenous vein by means of the cut down technique Oximetry data obtained early in the study demonstrated the presence of a left to right shunt at atrial level The catheter could be passed freely from the right atrium to the left atrium The mean pressure in the left atrium was 5 mm Hg and the mean pressure in the right atrium was 3 to 4 mm Hg

From the left atrium, the catheter was manipulated to the left ventricle Immediately upon the catheter s entering the left ventricle marked bradycardia occurred with ECG evidence of A V dissociation The catheter was withdrawn from the left ventricle Following administration of oxygen by face mask the cardiac rate and rhythm transiently returned to normal However, further attempts to manipulate the catheter in any of the cardiac chambers resulted in marked myocardial irritability A series of cardiac arrhythmias ensued including nodal bradycardia, A V dissociation and atrial flutter Following an episode of atrial flutter cardiac arrest occurred Vigorous resuscitative efforts were initiated

During the course of the resuscitative efforts the catheter was positioned in the right ventricle and a cine right ventriculogram was attempted Dr Amplatz is there any information that may be derived from this study?

Dr Amplatz This study was performed at a time when the patient had practically no cardiac output and therefore the study is of marginally diagnostic value The contrast medium was injected into a small trabeculated ventricular chamber which we felt was the right ventricle Considerable reflux into the right atrium and superior vena cava was present The aorta was opacified from the right ventricle There appeared to be a jet stream in the ascending aorta, suggesting the possibility of a stenotic semilunar valve The vessels of the aortic arch were not well visualized A small vessel arose from the arch at the level of the innominate artery which appeared to supply the right lung The source of blood flow to the left lung could not be identified However there appeared to be a vessel originating from the lesser curvature of the arch which subsequently opacified vessels in the left hilar region

Dr Stone The quality of the cine films was

Fig 4 *A* Heart and lungs from in front Solitary aortic trunk arises from right ventricle The aortic arch is left sided. First branch of aortic arch terminates as the right common carotid (*R C*) and distal ductal origin of right pulmonary artery (*R P.A*) Second branch of aortic arch is left common carotid artery (*L C*) Ductal origin of left pulmonary artery (*L P.A*) arises from aortic arch just proximal to left subclavian artery (*L.S*) *B* Posterior view showing trachea and descending aorta (*Des A*) (Esophagus has been removed) Branches of aortic arch shown from before backward are the left common carotid (*L C*) left subclavian (*L.S*) and right subclavian (*R.S*) arteries. In the natural state the right subclavian artery was directed toward the right

below quality for reproduction Resuscitative efforts were continued but were unsuccessful and the patient died in the catheterization laboratory Dr Lucas would you continue the discussion in light of the additional findings?

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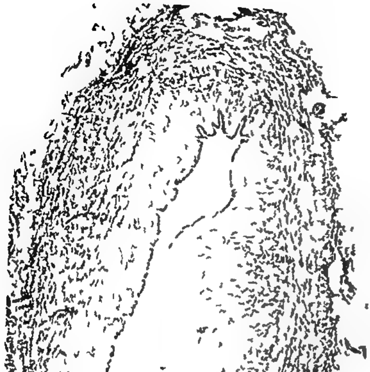

Fig 5 Photomicrograph of distal ductal origin of right pulmonary artery The structure is that of ductus arteriosus (Hematoxylin and eosin × 42)

origin of the vessel leading to the right pulmonary artery the wall of the vessel was thickened over a 5 mm length The upper lobe of the right lung was hypoplastic and the upper branch of the right pulmonary artery was narrow The second and the third branches of the vertex aortic arch were the left common carotid and the left subclavian artery respectively From the inferior aspect of the aortic arch distal to the level of origin of the left common carotid artery and proximal to the level of origin of the left subclavian artery arose the left ductus arteriosus Its origin was narrowed by a valvelike structure After a course of 6 mm the left ductus arteriosus became continuous with the left pulmonary artery The latter was 4 mm in diameter as it entered the hilus of the left lung The right subclavian artery arose distal to the left ductus arteriosus from the right posterior wall of the upper descending thoracic aorta and slightly distal to the origin of the left subclavian artery The right subclavian artery indented the posterior wall of the esophagus, ultimately to reach the right arm

A single pulmonary vein left the right lung was hypoplastic and entered the right atrium directly The left pulmonary veins were well developed and entered the left atrium normally The valve of the foramen ovale showed aneurysmal protrusion toward the left atrium In addition to those anomalies the heart showed a basal ventricular septal defect which measured about 4 by 7 mm and did not appear to have been obstructive The aorta arose primarily above the right ventricle The aortic valve was unicuspid, dysplastic, and stenotic Its orifice measured about 4 mm in diameter

The right and left ventricles were of equal thickness

Histologic examination of each lung revealed features of mild degrees of medial hypertrophy of the small muscular arteries In addition, multiple muscular pulmonary arteries were occluded by fibrin thrombi The capillaries were enlarged and tortuous The pulmonary parenchyma showed severe atelectasis and alveolar spaces contained macrophages and amniotic fluid material

Histologic examination of the vessel that led to the right pulmonary artery showed involutionary intimal thickening Its structure was that of a ductus arteriosus (Fig 5)

Dr Stone Dr Edwards will you comment on the pathologic and developmental aspects of this case?

Dr Jesse E Edwards The great vessels were characterized by the presence of a single vessel which had the characteristic of an aorta As no vestige of a pulmonary trunk was identifiable this state may be called solitary aortic trunk Other features of this case are both interesting and unusual These are (1) origin of each pulmonary artery from a homolateral ductus and (2) distal origin of each subclavian artery Normally the right and left pulmonary arteries each arise as a branch of the homolateral sixth aortic arch (Fig 6) These arches run between the aortic sac (later to be the ascending aorta and pulmonary trunk) ventrally and the homolateral dorsal aorta dorsally When the ventral portion of the sixth aortic arch is absent as when the pulmonary trunk does not form each pulmonary artery arises from the dorsal part of the homolateral sixth aortic arch (so called distal ductal origin)

In the presence of a left aortic arch as in the case under consideration the left ductus arises from the aortic arch On the right side, as the

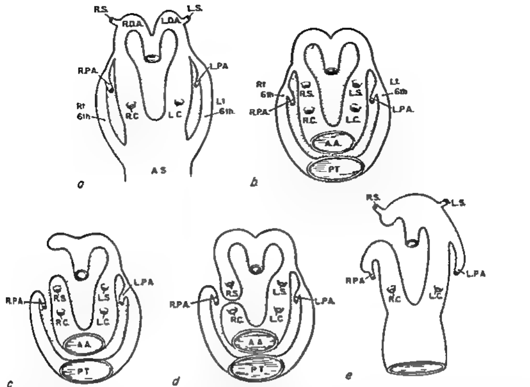

Fig 6 Diagrammatic portrayal of essentials of primitive aortic arch systems *A* The aortic sac (*A.S.*) gives rise to a sixth aortic arch on each side Each joins the homolateral dorsal aorta (*R.D.A.* *L.D.A.*) The diagram shows a stage in development wherein each carotid artery (*R.C.* *L.C.*) arises from the homolateral primitive aortic arch (fourth aortic arch) Each aortic arch joins the homolateral dorsal aorta from which the corresponding subclavian artery (*R.S.* *L.S.*) arises caudad to the entrance of the sixth arch Each pulmonary artery (*R.P.A.* *L.P.A.*) arises on a branch of the homolateral sixth arch *B* A later stage wherein the aortic sac has been divided into the ascending aorta (*A.A.*) and the pulmonary trunk (*P.T.*) On each side the subclavian artery has migrated onto the aortic arch, so as to arise at a level proximal to the dorsal entrance of the sixth arch *C* The normal formation of the innominate artery by interruption of the right dorsal aorta distal to the proximally migrated right subclavian artery is shown Beyond the origin of the right pulmonary artery the right sixth aortic arch is lost *D* The usual type of aberrant right subclavian artery results from interruption of the right dorsal aorta proximal to the right subclavian artery The distal part of the right sixth arch is lost as in the normal shown in *E* *E* Basis for findings in the case presented The aortic sac has not divided The proximal segment of each sixth arch has not formed so that each pulmonary artery arises from the dorsal segment of the homolateral sixth arch (distal ductal origin) The right subclavian artery is aberrant on the same basis as shown in *D* but this vessel has remained in a primitive position caudad to the dorsal part of the right sixth arch The latter gives rise to the right pulmonary artery and arises from the same stem as does the right common carotid artery

ght dorsal aorta becomes interrupted normally) form the innominate artery the right ductus if resent arises from the innominate artery Such situation basically occurred in this case with he exception that the right subclavian artery was aberrant and occupied a position distal to the ight sixth aortic arch (right ductus)

The distal portions of the subclavian arteries will now be considered It will be recalled that on each side the subclavian artery arose distal to the ductus In early development the subclavian artery arises from the homolateral dorsal aorta at a level distinctly caudad to the site of union of the sixth aortic arch with the dorsal aorta Normally the dorsal part of the right sixth aortic arch becomes lost beyond the site of origin of the right pulmonary artery so that no right ductus as such is identifiable On the left side the sixth aortic arch persists as the ductus and is easily identifiable as arising from the aortic arch at a level distal to the origin of the left subclavian artery from the aorta The relative changes in position between the left subclavian artery and the ductus is a striking phenomenon in normal

development. In our case the fact that the left ductus arose proximally to the left subclavian artery is to be taken as an arrest in the normal process of migration proximally of the left subclavian artery.

The distal position of the aberrant origin of the right subclavian artery relative to the right ductus arteriosus in this case may be explained as follows. Under normal circumstances, the right dorsal aorta becomes interrupted at a point caudad to the origins of the right subclavian artery and sixth aortic arch. This interruption yields an innominate artery. If a right ductus persists, it arises from the innominate artery. Aberrant right subclavian artery results from interruption of the right dorsal aorta proximal to the origin of the right subclavian artery so that this vessel arises from the dorsal rather than from the aortic arch. Usually in cases with aberrant right subclavian artery there is no right ductus identifiable. In the case presented, a right ductus was present and branched from the same arterial stem as did the right common carotid artery. The pattern present may be explained by the usual basis for formation of an aberrant right subclavian artery applying, but with lag in migration upward of the right subclavian artery.

We have observed retarded proximal migration of a subclavian artery in yet another condition. When coarctation of the aorta occurs between the left common and left subclavian arteries the left subclavian artery arises distal to the aortic insertion of the ductus arteriosus.

Final diagnosis: Ventricular septal defect, solitary aortic trunk, and ductal origins of pulmonary arteries.

-Management of the postoperative surgical patient

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Robert B Karp M D
, Ala

In recent years, as significant new knowledge of the pathophysiologic changes occurring in patients during and following open intracardiac procedures has become available optimal management of such patients has become a complex and often a multidisciplinary endeavor To effectively manage the patient in the postoperative period and achieve an optimal surgical result knowledge of the usual effects of extracorporeal circulatory support on the various organ systems and of those resulting abnormalities which may be life threatening and will require therapy is necessary

The major functional abnormalities that occur following cardiac surgical procedures employing extracorporeal support are primarily related to (1) the degree of preoperative dysfunction of the various organ systems and the functional reserve of these systems (2) the duration and adequacy of the period of extracorporeal support and (3) the completeness of repair of the specific cardiac or vascular abnormalities To simplify postoperative care following a major cardiac surgical procedure the patient may be considered as an integrated system composed of separate but interrelated subsystems (i e cardiovascular pulmonary renal neurological gastrointestinal and endocrine) The management of such a patient can be effectively accomplished with a systems analysis approach With this approach as proposed by Kirklin [1] each organ system is analyzed separately by assessing all available information relative to the present performance of the system the adequacy of this performance relative to the requirements of the patient as an integrated system and the used and unused reserves of the system This report will focus on the major disturbances in organ system function that occur following major cardiac surgical procedures and their management

From the Di ision of Cardio asc lar and Thor cic Su gery Department of Surgery University of Alabama Medic l Center Birmingham Ala.

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Cardiovascular system

Impaired cardiac performance following open intracardiac operations manifested chiefly by low cardiac output is associated with significant mortality and morbidity rates in the early postoperative period [2,3] When the patient is restless or agitated with cool moist and cyanotic extremities weak or absent peripheral pulses and low urine flow early postoperatively the diagnosis of low cardiac output can be made with relative certainty even in the presence of a normal blood pressure Unfortunately a number of patients with low cardiac output do not manifest these clinical signs Thus actual measurement of cardiac output is required in many circumstances to accurately assess cardiac function The range for cardiac output in the normal resting adult is approximately 2 4 to 4 4 L /min /M² of body surface area (mean 3 5) [4] Mean values for cardiac output following a variety of open intracardiac operations are shown in Table I and vary with the type of operation

The consequences of an abnormally low cardiac output when there is evidence of increased sympathetic activity have been documented by Dietzman and associates In a series of 25 patients with early postoperative measured cardiac indices of less than 3 0 L /min /M² they

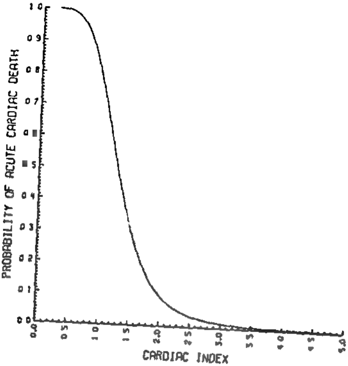

Fig 1 Probability of death from acute cardiac failure from the average cardiac index (L/min/M) of 139 infants and children in the early postoperative period (From Parr G V S Blackstone E H and Kirklin J W Cardiac performance and mortality early after intracardiac surgery in infants and young children Circulation 51 867 197 Modified and reproduced by permission of the American Heart Association)

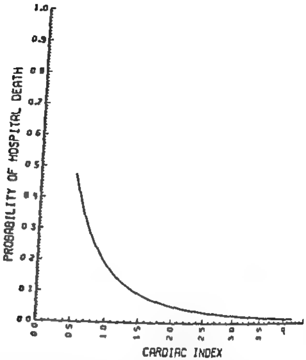

Fig 2 Probability of death from acute cardiac failure from the average cardiac index (L/min/M) of 1?5 patients following mitral valve replacement (From Applebaum, A Kouchoukos, N T Blackstone E H and Kirklin J W The early risks of open mitral valve surgery Am J Cardiol 3? 201, 1976 Reproduced by permission of the American College of Cardiology the Dun Donnelley Publishing Corporation)

noted a significant difference in survival between those patients with cardiac outputs between 2 0 and 3 0 L/min/M who had normal peripheral vascular resistance and adequate tissue perfusion, and those with outputs of less than 2 0 L/min/M² who had evidence of increased sympathetic activity (increased peripheral vascular resistance reduced tissue perfusion increased serum catecholamine levels) Even though cardiac output was slightly below normal values in the former group of patients, it was adequate to meet the metabolic requirements for the various organ systems In other studies deaths from acute cardiac failure have occurred most commonly in patients with a low value for mean cardiac output early postoperatively[4,5] In infants and small children following a variety of cardiac operations an average measured cardiac index of less than 2 0 L/min/M² in the early postoperative period was associated with a greater than 10 per cent probability of death from acute cardiac failure (Fig 1)[4] In adult patients following mitral valve replacement a mean postoperative cardiac index of 1 5 L/min/M² or less was associated with a 10 per cent or greater probability of death (Fig 2)[5] The probability of death rose steeply in both groups at indices below these values

In patients with low cardiac output and impaired left ventricular function as evidenced by abnormally elevated mean left atrial and left ventricular end diastolic pressures the mortality and morbidity rates early after operation are also significantly increased Fig 3 shows the cardiac outputs and mean left atrial pressures of 30 adult patients in the first 4 hours following a variety of cardiac surgical procedures These data were obtained in a period when low cardiac output was not systematically treated Of 16 patients with cardiac indices less than 2 2 L/min/M² and left atrial pressures greater than 15 mm Hg three died within 24 hours of operation of irreversible ventricular arrhythmias and two died within ? weeks of operation of ventricular arrhythmias Both of the latter patients continued to have low cardiac output during this period Two additional patients had episodes of ventricular fibrillation but survived Among the 14 patients with lower left atrial pressures and generally higher cardiac indices there was only one postoperative death Thus evidence for impaired cardiac performance should be actively sought in order to institute

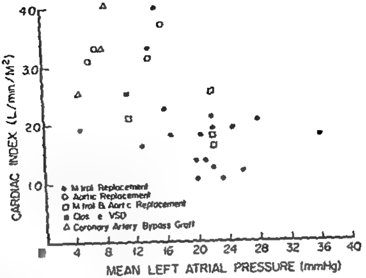

Fig 3. Comparison of cardiac index and mean left atrial pressure in 30 adult patients in the first 4 hours after open intracardiac operations.

able I Average cardiac output* after open intracardiac operations

Type of operation†	No of ca	Cardiac output mean (and range) after operation			
		Chest open ½ hr after bypa s	? 4 hr	24 hr	49 hr
Repair					
ASD with normal pulmonary vascular resistance	5	3 0 (2 1 3 9)	3 4 (? 4 4 4)	3 0 (2 3-4 0)	3.5 (2.9 3)
VSD with normal pulmonary vascular re sistance	–	3 8 (3 2 3)	3 5 (2 9 4 .)	? ? (? , 4 4)	3 4 (2 – 4 4)
VSD w h moderately elevated pulmo nary vascular resistance	3	3 (3 4 4 0)	3 7 (? 9 4 4)	3 0 (1 9 3 6)	2 9 (2 3 3.5)
Tetralogy of Fallot	15	2 5 (? 0 3 5)	? 9 (0- 5)	2 2 (1 6-3 ?)	? ? (1 – 5 2)
Replacement					
Aortic valve with S E prosthesis		? (1 6 3 1)	? 4 (1 4 3 8)	? 8 (0-4 5)	3 2 (2 3-4.1)
Mitral valve with S-E prosthesis	12	5 (1 1 4 1)	1 – (1 0 ? 6)	1 5 (0 9 3 0)	2 ? (1 2 3.5)

*Normal lues = 3.5 (+ 0) L m M f body fac
†ASD = atrial septal d fect VSD = entricul septal defect S E = St rr Edwards.
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appropriate therapy and minimize early deaths and morbidity

Routine maintenance measures Certain parameters to assess the function of the cardiovascular system should be measured routinely in the early postoperative period Arterial pressure is obtained with an indwelling cannula usually placed percutaneously in the radial (or alternately the femoral or brachial) artery Heart rate and rhythm are determined from standard electrocardiographic leads Left atrial and right atrial (central venous) pressures are determined from fine polyvinyl catheters placed at the time of operation Measurements of arterial and atrial pressures (in millimeters of mercury) are obtained at 5 to 15 minute intervals in the first 24 to 48 hours following operation In our experience the use of indwelling arterial and cardiac catheters for this

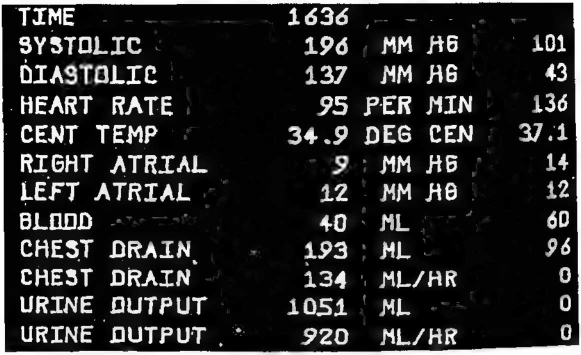

Fig 4 Oscilloscopic display of hemodynamic data from a 3 second interval obtained from two patients connected to an automated monitoring system Chest drainage and urine output are expressed as total milliliters and as milliliters for the previous clock hour (From Kouchoukos N T Sheppard L C and Kirklin J W Automated patient care following cardiac surgery *in* Brest A N editor Cardiovascular clinics vol 3 No 3 Philadelphia 1971 F A Davis Company p 109 [7] Reproduced by permission of the F A Davis Company)

period of time has been associated with an extremely low incidence of complications and we utilize them routinely in all patients undergoing surgical procedures employing extracorporeal circulatory support The volume of drainage from pericardial mediastinal and pleural tubes the amount of blood infused and the output of urine from a uretheral catheter are recorded at hourly intervals Arterial blood gas analyses are obtained as often as necessary to assure optimum gas exchange and acid base balance (see below)

Cardiac output is usually determined by the indicator dilution technique injecting indocyanine green dye into the left atrial catheter and sampling from the arterial catheter or alternately, injecting dye into the right atrial catheter and sampling from a catheter placed in the pulmonary artery at the time of operation The latter system is preferred when the left sided cardiac chambers are large or the cardiac output is low to minimize distortion of the dilution curves and errors in the calculated value for cardiac output [7] In infants and small children, dye is injected into the right atrium and blood is withdrawn from the radial or brachial artery to allow adequate time for mixing [8] With the use of appropriate densitometers and portable or large computers, cardiac output is calculated according to the Stewart Hamilton formula [9] When the thermal dilution technique is employed cold saline is used as the indicator and is injected into the right atrium with measurement of temperature change of the blood in the pulmonary artery by means of a thermistor tipped catheter This method has the advantage of allowing repeated determinations of cardiac output without the need for withdrawal of blood [1] Determination of stroke volume and cardiac output from the arterial pressure pulse contour has not proved reliable enough in the postoperative period to routinely supplant the techniques outlined above [11]

All of the above measurements can be obtained, analyzed, and displayed automatically with a digital computer as shown in Fig 4 Use of such an automated system has greatly facilitated the management of patients following cardiac surgical procedures [12] It has provided data that can be retrieved more rapidly and that are more accurate than those obtained by conventional manual techniques [13]

Arterial pressure is generally thought to be a reliable indicator of cardiac function postoperatively If arterial hypotension is present (systolic arterial pressure less than 70 to 80 mm Hg cardiac function is generally suboptimal If the arterial pressure is normal or above norm

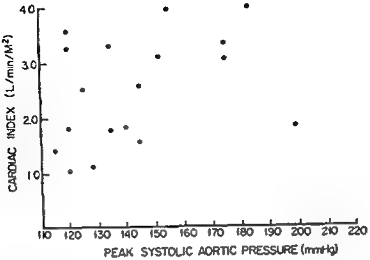

Fig 5 Comparison of cardiac index and peak systolic aortic pressure in 25 adult patients in the first 4 hours after open intracardiac operations.

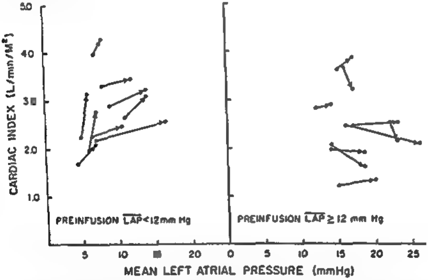

Fig 6 Effect of elevation of left atrial pressure by blood infusion on cardiac index in adult patients early after open intracardiac operations (heart rate constant) (Left) Nine patients with preinfusion mean left atrial pressures (LAP) of less than 12 mm Hg (Right) Nine patients with preinfusion mean left atrial pressures of greater than 12 mm. Hg.

however the cardiac output may be high normal or low (Fig 5) Central venous (right atrial) pressure does not demonstrate a consistent relationship to cardiac output blood volume deficit or the response to blood replacement postoperatively In our experience measurement (or estimate) of cardiac output combined with measurement of arterial pressure and mean left atrial pressure which in the absence of either stenosis or incompetence of the mitral valve approximates left ventricular end diastolic pressure[11] allows a more accurate assessment of cardiac function and the response to various therapeutic interventions than does measurement of arterial and central venous pressures If a left atrial catheter is not available the pulmonary arterial wedge or diastolic pressure can be measured from a catheter placed in the pulmonary artery (Swan Ganz) and thus approximates the left ventricular filling pressure

Table II Hospital deaths following valve replacement according to preoperative functional class

Valve(s) replaced	Preoperative functional class*	No of patients	Hospital deaths	
			No	%
Mitral[25]	III	109	3	3
	IV	24	4	17
Aortic and mitral[2]	III	180	17	9
	IV	52	15	29
Tricuspid[27] (isolated or with multiple replacements)	III	60	10	17
	IV	27	9	33

* New York Heart Association classification

Etiology, diagnosis and management of impaired cardiac performance in the postoperative period

Hypovolemia. Inadequate blood volume is a frequent cause of impaired cardiac performance early after operation. The magnitude of the blood volume deficit during this period depends on several factors, the most important being (1) the adequacy of volume replacement at the termination of the operative procedure, (2) the degree of vasoconstriction present, particularly of the large venous capacitance vessels, and (3) the volume of blood lost as mediastinal drainage relative to the volume of blood replaced. In general, blood is infused from the pump oxygenator at the termination of the perfusion to achieve a mean left atrial pressure of 14 to 18 mm Hg in adults and 10 to 14 mm Hg in infants and children. These levels of left atrial pressure result in optimal stretching of the sarcomeres (preload) and optimal stroke volume, but do not produce pulmonary congestion or edema. The left and right atrial pressures generally decrease to more normal levels in the early postoperative period.[11] The ultimate values for right and left atrial pressures are determined primarily by the volume of blood in the systemic and pulmonary venous beds, the venous tone of these two systems, and the pressure volume characteristics of the left- and right-sided cardiac chambers. In adult patients with valvular heart disease, blood volume is decreased and whole body venous tone increased following operation.[18] These changes are maximal 24 to 48 hours following operation and approach the preoperative values by the fourth postoperative day.

As noted previously, central venous (or right atrial) pressure does not demonstrate a consistent relationship to blood volume deficit or the response to blood replacement following operation. Measurement of mean left atrial pressure (or pulmonary wedge or diastolic pressure) is the most reliable guide to the adequacy of volume replacement during this period. The effects of blood infusion on left atrial pressure and cardiac output early after surgical procedures for acquired heart disease are shown in Fig 6. In nine patients with normal mean left atrial pressures (less than 12 mm Hg), infusion of blood to increase left atrial pressure an average of 3.4 mm Hg produced a statistically significant increase in cardiac index (2.52 to 2.93 L/min/M²) while heart rate remained constant. In nine patients with mean left atrial pressures before blood infusion of greater than 12 mm Hg (mean 15.6 mm Hg), comparable increases in left atrial pressure were produced, but cardiac index did not increase, and the mean value actually decreased (2.58 to 2.41 L/min/M²).[19] Thus, if cardiac output is low and left atrial pressure is low or normal (less than 12 to 14 mm Hg), infusion o[f] blood will generally increase cardiac output early postoperatively. If left atrial pressure is already elevated above this level, further augmentation o[f] blood volume and filling pressure does not usually increase cardiac output. Recent studies of le[ft] ventricular pressure volume relations in patient[s] with mitral valvular disease indicate that a[t] filling pressures above 14 mm Hg minima[l] increases (less than 3 per cent) in calculated le[ft] ventricular fiber length (preload) are produce[d] while at the same time marked increases in le[ft] ventricular wall tension result, particularly i[n] dilated ventricles.[9] Studies on the effects o[f] volume infusion in patients with acute myoca[r]dial infarction have also shown a lack of improv[e]ment in cardiac output when left ventricul[ar] filling pressures are elevated above 14 to 18 mm Hg.[1]

Cardiac tamponade. Persistent bleeding in[to] the pericardial cavity and mediastinum resultin[g] in cardiac tamponade is a relatively uncommo[n] but serious cause of impaired cardiac performan[ce] following operation. Bleeding of sufficient quan[ti]tity to require reoperation occurs in approximat[e]ly 3 per cent of patients undergoing cardi[ac] operations.[2] A somewhat higher incidence [of] postoperative bleeding has been noted in patien[ts]

-h cyanotic heart disease and with right sided -diac failure the latter presumably depressing -patic function and the synthesis of several -tting factors. Cardiac tamponade generally -omes apparent in the early postoperative -iod but can be delayed in its presentation for -to 2 weeks following operation particularly -anticoagulants are being administered

The diagnosis of cardiac tamponade may at -mes be difficult to make with certainty Signifi -nt drainage from the mediastinal tubes -mbined with a trend toward equalization and -adual increase of the right and left atrial pres -res, strongly suggests the presence of cardiac -mponade Subsequently arterial hypotension -d clinical evidence of low cardiac output may -velop A chest roentgenogram often demon -strates an increase in the mediastinal silhouette -reatment consists of urgent operation to -acuate clot and identify and control the point -points of bleeding If the bleeding is general -ed, deficiencies of various clotting factors (plate -ts, factors V and VIII and fibrinogen) must be -ught by the appropriate tests Administration -f fresh frozen plasma fresh whole blood and -latelet and plasma concentrates is indicated -hen deficiencies of these substances are demon -trated The use of heparin for disseminated -ntravascular coagulation or ε aminocaproic -cid for excessive fibrinolysis is generally not -ndicated since these problems are generally self -imited.

Myocardial dysfunction Total cardiac per -ormance can be significantly affected postopera -tively by several mechanisms which impair -myocardial function

PREOPERATIVE CARDIAC DYSFUNCTION Ab -normalities of myocardial function may be present preoperatively in patients with both acquired and congenital heart disease and these may persist or actually become more severe following operation In our experience with patients following mitral tricuspid or multiple valve replacement the severity of preoperative cardiac disability as reflected by the functional class, clearly affects the hospital mortality rate (Table II)[2, 7] Pre existing myocardial dysfunc tion is probably an important contributing factor to the low cardiac output state observed following mitral valve replacement

Impairment of myocardial contractility has been demonstrated preoperatively in patients with aortic and mitral valvular disease[28, 29] and in patients with coronary atherosclerotic heart disease particularly those with predominant symptoms of congestive failure [30-31] Higher opera tive and late mortality rates have been observed in the latter group of patients following myocar dial revascularization in contrast to patients with more normal ventricular function [30, 32] Follow up studies of patients following valve replacement or coronary bypass surgery have demonstrated that the preoperative abnormalities in myocardial function often persist and may become even more severe in some patients despite correction of the valvular coronary arterial or myocardial le sions [28, 30, 33]

INTRAOPERATIVE MYOCARDIAL INJURY Myo cardial injury can occur during cardiopulmonary bypass and if severe or if imposed upon myocar dium that is already abnormal (i e left ventric ular hypertrophy left ventricular fibrosis coro nary arterial occlusive disease) can significantly impair cardiac performance in the postoperative period Ischemia, hemorrhage, and necrosis of the myocardium particularly of the inner layers of the left ventricular wall have been observed in patients dying after cardiopulmonary bypass many of whom had low cardiac output postoper atively [4, 6] Studies of myocardial metabolism and measurement of specific enzymes to detect myocardial injury indicate that myocardial damage of varying severity occurs in many patients during or following operations in which cardiopulmonary bypass is employed irrespective of the technique of myocardial preservation utilized during the procedure [33]

The presence of markedly hypertrophic left ventricular myocardium may predispose to severe ischemic myocardial injury following cardiopul monary bypass A small contractive left ventricle that does not eject effectively has been observed in patients of this type and has been termed the "stone heart" This type of myocardial injury has been observed following normothermic cardioplegia and in our own experience follow ing hypothermic coronary perfusion as methods of myocardial preservation The incidence of this complication has apparently been reduced follow ing the use of hypothermic cardioplegia [4] and our experience in patients with aortic valve replace ment supports this observation

Embolization of air to the coronary arteries can occur during operations in which the ascending

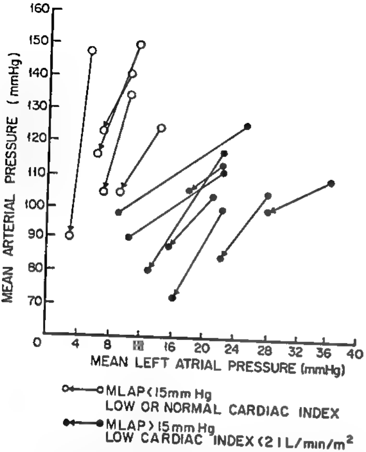

Fig 7A Effect of infusion of trimethaphan camsylate (Arfonad) on mean arterial pressure and mean left atrial pressure in patients within 6 hours after intracardiac operations The eight patients in the group with poor cardiac performance (cardiac index less than 2 1 L/min/M mean left atrial pressure greater than 15 mm Hg) had undergone mitral or mitral and aortic valve replacement (From Kouchoukos N T Sheppard L C and Kirklin J W Effect of alterations in arterial pressure on cardiac performance early after open intracardiac operations J Thorac Cardiovasc Surg 64 563 1972 Reproduced by permission of The C V Mosby Company)

aorta or left sided heart chambers are opened and can impair myocardial contractility [42] Embolization of blood element aggregates into the myocardial vasculature may also affect myocardial function Injury to the coronary arteries during the operative procedure (i e by direct cannulation, inadvertent injury to the aberrant anterior descending coronary artery during repair of tetralogy of Fallot injury to the left circumflex coronary artery during replacement of the mitral valve, and during myocardial revascularization) can produce myocardial infarction and severely impair cardiac performance

Residual Cardiovascular Disease The presence of residual cardiovascular abnormalities may also contribute to impaired myocardial function following operation Examples of this include the presence of significant tricuspid valvul incompetence following mitral and aortic val replacement,[14] aortic valvular incompetence fo lowing mitral valve replacement,[43] corona arterial occlusive disease following valve replac ment,[44, 45] and the persistence of significa pulmonary arterial hypertension following co rection of left to right shunts [46] The inadequa repair of congenital or acquired lesions (i.e incomplete relief of right ventricular outflo obstruction in tetralogy of Fallot, incomple closure of ventricular septal defects, incomplete correction of valvular stenosis or incompetence and perivalvular leaks) may also impair myocar dial function postoperatively Careful preopera tive and intraoperative evaluation should allow detection and appropriate treatment of most myocardial and valvular lesions When there ■ evidence for significant impairment of cardiac performance postoperatively prompt reoperation should be considered in any patient in whom correctable residual lesions are present

Impaired Myocardial Contractility If evidence for impaired myocardial contractility ■ present use of pharmacologic agents which have positive inotropic effects is indicated Isoproterenol is an effective agent since it exerts a chronotropic as well as an inotropic action on the myocardium and cardiac output can be augmented by both these mechanisms In addition, it can produce peripheral vasodilatation which may be beneficial if there is significant vasoconstriction Tachycardia and ventricular arrhythmias can result with infusion of this drug, however and not infrequently limit its use Although isoproterenol can produce an increase ■ cardiac output postoperatively myocardial oxygen demand is also increased and anaerobic myocardial metabolism may result [47]

Epinephrine is also ■ useful agent postoperatively particularly when arterial hypotension is present If infused in sufficient amounts epinephrine will increase myocardial contractility and peripheral vascular resistance and, thus increase cardiac output and arterial pressure [4] In smaller doses it may actually result in a fall in peripheral vascular resistance due to the beta adrenergic effect on blood vessels [49] Dopamine (Inotropin) a naturally occurring catecholamine with inotropic and chronotropic effects on myocardium has been shown to be effective in the management of some patients following

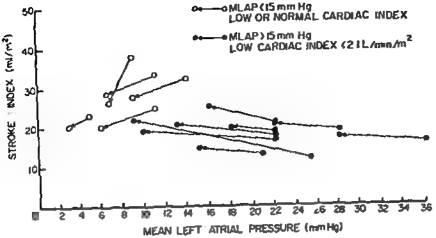

Fig 7B Effect of Arfonad on mean left atrial pressure and stroke index See legend and credit line under Fig *A*

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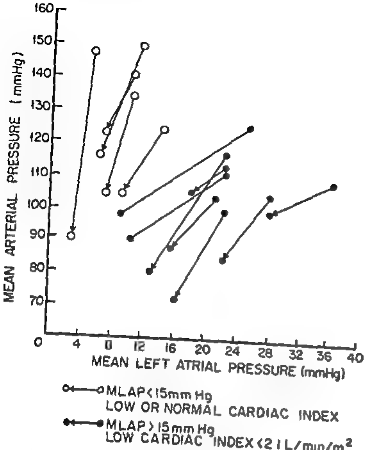
Digitalis preparations should be used postoper tively to improve myocardial contractility and or treatment of specific arrhythmias (see below) Rapidly acting preparations (digoxin deslano ide ouabain) should be administered postopera tively when there is evidence of impaired myocar ial function and there are no contraindications o their use These agents are often used in onjunction with catecholamine infusions As an ppropriate blood level of digitalis is obtained the atecholamine drugs may be tapered and discon inued Digitalis preparations should be adminis ered cautiously taking into account the status of igitalization preoperatively as well as the resence of hypokalemia and alkalosis which may increase the sensitivity of the patient to usual maintenance doses We routinely discon tinue digitalis preparations 24 to 48 hours before operation to minimize the occurrence of intra operative and postoperative arrhythmias

The use of propranolol (Inderal) preoperatively in patients with ischemic heart disease particu larly in large doses (greater than 80 to 100 mg per day) has been associated with severely impaired cardiac performance following coronary arterial surgery While discontinuation of the drug before operation is preferable acute myocardial infarction has occurred under these circum stances[33] Accordingly tapering of the drug should be done cautiously and in our opinion patients who are receiving up to 80 to 100 mg of Inderal per day can be operated upon without significant difficulty If myocardial function is severely depressed postoperatively in patients who have been receiving propranolol isoprotere nol calcium and digitalis may be effective in improving myocardial contractility

IMPEDANCE TO LEFT VENTRICULAR EJECTION Increased impedance to left ventricular ejection which results in an increase in systolic wall tension (afterload) has been shown to reduce stroke volume and left ventricular stroke work in patients with diseased myocardium In post operative adult patients with elevated mean arterial pressure high peripheral vascular resist ance and low cardiac output improvement in cardiac output has been achieved by reduction of arterial pressure In a group of patients with high mean arterial pressure (greater than 100 mm Hg) and evidence of impaired cardiac performance (cardiac index less than 2 1 L/min/M and mean left atrial pressure greater than 15 mm Hg) infusion of Arfonad (trimetha phan camsylate) a ganglionic blocking and vasodilating agent produced a significant in crease in stroke index and cardiac output in all patients studied which averaged 18 and 15 per cent respectively (Fig 7) Comparable reduction of arterial pressure in patients with higher cardiac indices and lower left atrial pressures suggesting



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RESIDUAL CARDIOVASCULAR DISEASE The presence of residual cardiovascular abnormalities may also contribute to impaired myocardial function following operation Examples of this include the presence of significant tricuspid valvular incompetence following mitral and aortic valve replacement[43] aortic valvular incompetence following mitral valve replacement,[43] coronary arterial occlusive disease following valve replacement[44, 45] and the persistence of significant pulmonary arterial hypertension following correction of left to right shunts[46] The inadequate repair of congenital or acquired lesions (i.e. incomplete relief of right ventricular outflow obstruction in tetralogy of Fallot, incomplete closure of ventricular septal defects incomplete correction of valvular stenosis or incompetence, and perivalvular leaks) may also impair myocardial function postoperatively Careful preoperative and intraoperative evaluation should allow detection and appropriate treatment of most myocardial and valvular lesions When there is evidence for significant impairment of cardiac performance postoperatively, prompt reoperation should be considered in any patient in whom correctable residual lesions are present

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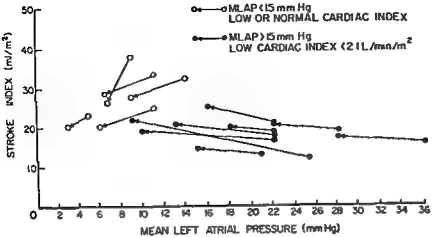

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Impedance to Left Ventricular Ejection Increased impedance to left ventricular ejection which results in an increase in systolic wall tension (afterload) has been shown to reduce stroke volume and left ventricular stroke work in patients with diseased myocardium[5] In postoperative adult patients with elevated mean arterial pressure high peripheral vascular resistance and low cardiac output improvement in cardiac output has been achieved by reduction of arterial pressure[8] In a group of patients with high mean arterial pressure (greater than 100 mm Hg) and evidence of impaired cardiac performance (cardiac index less than 2.1 L/min/M²) and mean left atrial pressure greater than 15 mm Hg) infusion of Arfonad (trimethaphan camsylate) a ganglionic blocking and vasodilating agent produced a significant increase in stroke index and cardiac output in all patients studied which averaged 18 and 15 per cent respectively (Fig 7) Comparable reduction of arterial pressure in patients with higher cardiac indices and lower left atrial pressures suggesting

more normal left ventricular function, resulted in a decrease in stroke volume, presumably as a result of decrease in left ventricular filling pressure (preload). We have made similar observations using sodium nitroprusside, a potent vasodilator, in adult patients with significantly impaired cardiac function. More recently, we have used sodium nitroprusside in infants following intracardiac surgery and with reduction of mean arterial pressure to normal levels have observed a significant increase in cardiac output and a reduction in the markedly elevated peripheral vascular resistance in all patients studied.[56]

Phentolamine (Regitine) produces hemodynamic effects similar to those of trimethaphan or nitroprusside but may produce tachyarrhythmias. Phenoxybenzamine (dibenzyline), an alpha adrenergic blocking agent, has also been shown to improve cardiac output in patients with impaired cardiac performance postoperatively.[1] When administered intravenously, however, maximal activity is not obtained for several hours and its effect may persist for several days. We presently prefer trimethaphan or sodium nitroprusside because of their rapid onset and short duration of action. The infusion rates of these agents can be adjusted relatively easily to achieve the desired reduction in arterial pressure.

Use of vasodilating agents to reduce arterial pressure and impedance to left ventricular ejection should be considered in postoperative patients when cardiac index is low and left atrial pressure, mean aortic pressure and peripheral vascular resistance are elevated. Reduction of arterial pressure under these circumstances allows more effective emptying of the left ventricle and may, with reduction of left ventricular end diastolic pressure, reduce left ventricular wall stress and allow more efficient perfusion of the subendocardial area of the left ventricle.[20, 57, 58] Reduction in left ventricular systolic pressure will also reduce myocardial oxygen consumption. If cardiac output remains low and the filling pressure high following administration of these vasodilating agents, addition of inotropic drugs, such as epinephrine, dopamine, or isoproterenol, may be effective in increasing cardiac output.

INTRA AORTIC BALLOON COUNTERPULSATION. Assistance of the failing circulation with the intra aortic balloon counterpulsation device has been employed in patients in whom cardiopulmonary bypass cannot be discontinued without hemodynamic deterioration or in patients who deteriorate later in the postoperative period. Intra aortic balloon counterpulsation reduces left ventricular work and oxygen consumption and may improve myocardial perfusion. The majority of the patients in whom this device has been used have been those with severe coronary artery disease and evidence for severely impaired left ventricular function. It has also been applied in a small number of patients following other cardiac surgical procedures such as single or multiple valve replacement. The indications for use of this device are not completely defined, but in general it has been employed when there is evidence of deterioration of the hemodynamic state (mean aortic pressure less than 80 to 90 mm Hg, mean left atrial or left ventricular end diastolic pressure greater than 25 mm Hg, and low cardiac output). The patients have usually received maximal pharmacologic support. In three series in which the device was employed following cardiac surgery, the hospital mortality rate ranged between 40 and 50 per cent, and 33 to 43 per cent of the patients were long term survivors.[59, 61] While these results are not optimal, it must be recognized that the majority of these patients would have died without the period of circulatory support. The favorable experience in these series may result in expanded use of the device postoperatively, possibly as a substitute for catecholamine support which may have detrimental effects, particularly in patients with ischemic myocardium.[47]

Acid base and electrolyte abnormalities. Metabolic acidosis occurs infrequently following extracorporeal circulatory support with the currently used pump oxygenator systems and priming techniques. When metabolic acidosis is present postoperatively, it may reflect inadequate perfusion during bypass, particularly if the period of bypass was prolonged. More commonly, metabolic acidosis results from low cardiac output postoperatively with poor tissue perfusion. Since metabolic acidosis may adversely effect myocardial function,[62] it should be treated vigorously. Improvement in cardiac output is obviously an important aspect of therapy. Vasopressor agents may be more effective in the treatment of low cardiac output if the acidosis is corrected.[62] Arterial hypoxemia, if present, should also be corrected to assure adequate oxygen delivery to the tissues.

Alkalosis is more often present postoperatively than acidosis Metabolic alkalosis may result from the citrate ion present in ACD blood and is often compounded by the respiratory alkalosis which occurs in patients who are receiving assisted ventilation Patients who require ventilatory support should have careful control of the ventilator to avoid severe respiratory alkalosis (arterial P_{CO_2} less than 30 mm Hg and arterial pH above 7 60) Alkalosis above this level may impair myocardial contractility [43]

Low serum potassium concentrations are frequently present following procedures employing cardiopulmonary bypass and may result in arrhythmias which can significantly impair cardiac performance (see below) Preoperative diuretic therapy may deplete total body potassium and potassium ion should be administered preoperatively in patients who have been on long term diuretic therapy if serum potassium concentration is low The diuresis which occurs following cardiopulmonary bypass particularly when hemodilution has been employed promotes the urinary excretion of potassium Respiratory alkalosis resulting from mechanical ventilation reduces the serum potassium concentration which may be reduced further by the increase in urinary potassium excretion [6] To minimize these potassium losses diuretic therapy should be discontinued several days before operation if possible In addition potassium chloride should be administered postoperatively when potassium levels are below 3 5 mEq per liter to minimize the occurrence of arrhythmias

Calcium ion may exert a positive inotropic effect on myocardium and if serum calcium levels are low in the presence of a low cardiac output calcium should be administered This is of particular importance when large amounts of citrated blood are infused since serum calcium may be inactivated by the citrate

Abnormalities of rate and rhythm Arrhythmias occur commonly following cardiac surgical procedures and though generally transient and well tolerated may occasionally impair cardiac performance This is particularly true if there are other mechanisms operative which are also contributing to impaired cardiac function Factors which predispose to the development of arrhythmias following cardiac procedures include electrolyte imbalance (particularly low serum potassium) metabolic acidosis hypoxemia digitalis excess surgical trauma and pre existing cardiac disease [5] Such abnormalities when present early postoperatively should be corrected promptly when possible

Placement of epicardial wires at the time of operation allows for accurate diagnosis of arrhythmias following operation and for therapy by pacing These wires should be placed both on the right atrium and the left or right ventricle and should preferably be placed in pairs 0 5 to 1 0 cm apart to allow accurate recordings to be made from them and to allow the use of low current stimulation if necessary [44]

Arrhythmias affect cardiac performance chiefly by their effect on heart rate Arrhythmias associated with bradycardia often result in decrease in cardiac output even though there may be an initial compensatory increase in stroke volume Ventricular extrasystoles may also occur at slow ventricular rates and further impair cardiac function Arrhythmias resulting in tachycardia (greater than 120 to 140 per minute) decrease cardiac output by impairment of diastolic filling with resultant reduction in stroke volume This may be an important factor in patients following valve replacement since the function of some prosthetic valves is significantly impaired at rapid heart rates Perfusion of the myocardium particularly the subendocardial layers may also be impaired with tachycardia due to the reduction of coronary blood flow during diastole

Supraventricular arrhythmias

Sinus tachycardia This not infrequently occurs following cardiac surgical procedures and is generally transient If myocardial function is normal and the rate is not excessive it is usually well tolerated Occasionally the rate may be excessively rapid (greater than 150 to 160 beats per minute) and under these circumstances therapy may be required to improve cardiac function Obvious causes for tachycardia (hypovolemia fever pericardial tamponade) must be sought and appropriately treated Neostigmine (Prostigmin) in small doses (0 5 to 1 0 mg) may be successful in slowing the rate Digitalis is also effective particularly if the tachycardia originates from an ectopic focus since it should slow the rate of the ectopic pacemaker and prolong atrioventricular conduction thus slowing the ventricular rate

Paroxysmal atrial tachycardia This can often be interrupted by maneuvers which increase

more normal left ventricular function, resulted in a decrease in stroke volume, presumably as a result of decrease in left ventricular filling pressure (preload) We have made similar observations using sodium nitroprusside a potent vasodilator, in adult patients with significantly impaired cardiac function More recently we have used sodium nitroprusside in infants following intracardiac surgery and with reduction of mean arterial pressure to normal levels, have observed a significant increase in cardiac output and a reduction in the markedly elevated peripheral vascular resistance in all patients studied [56]

Phentolamine (Regitine) produces hemodynamic effects similar to those of trimethaphan or nitroprusside but may produce tachyarrhythmias Phenoxybenzamine (dibenzyline) an alpha adrenergic blocking agent has also been shown to improve cardiac output in patients with impaired cardiac performance postoperatively [1] When administered intravenously, however maximal activity is not obtained for several hours and its effect may persist for several days We presently prefer trimethaphan or sodium nitroprusside because of their rapid onset and short duration of action The infusion rates of these agents can be adjusted relatively easily to achieve the desired reduction in arterial pressure

Use of vasodilating agents to reduce arterial pressure and impedance to left ventricular ejection should be considered in postoperative patients when cardiac index is low and left atrial pressure, mean aortic pressure and peripheral vascular resistance are elevated Reduction of arterial pressure under these circumstances allows more effective emptying of the left ventricle and may, with reduction of left ventricular end diastolic pressure reduce left ventricular wall stress and allow more efficient perfusion of the subendocardial area of the left ventricle [10,57,58] Reduction in left ventricular systolic pressure will also reduce myocardial oxygen consumption If cardiac output remains low and the filling pressure high following administration of these vasodilating agents addition of inotropic drugs, such as epinephrine, dopamine or isoproterenol, may be effective in increasing cardiac output

Intra aortic Balloon Counterpulsation Assistance of the failing circulation with the intra aortic balloon counterpulsation device has been employed in patients in whom cardiopulmonary bypass cannot be discontinued without hemodynamic deterioration or in patients who deteriorate later in the postoperative period. Intra aortic balloon counterpulsation reduces left ventricular work and oxygen consumption and may improve myocardial perfusion The majority of the patients in whom this device has been used have been those with severe coronary artery disease and evidence for severely impaired left ventricular function It has also been applied in a small number of patients following other cardiac surgical procedures such as single or multiple valve replacement The indications for use of this device are not completely defined, but in general it has been employed when there is evidence of deterioration of the hemodynamic state (mean aortic pressure less than 80 to 90 mm Hg mean left atrial or left ventricular end diastolic pressure greater than 25 mm Hg and low cardiac output) The patients have usually received maximal pharmacologic support In three series in which the device was employed following cardiac surgery, the hospital mortality rate ranged between 40 and 50 per cent, and 38 to 49 per cent of the patients were long term survivors [59-61] While these results are not optimal it must be recognized that the majority of these patients would have died without the period of circulatory support The favorable experience in these series may result in expanded use of the device postoperatively, possibly as a substitute for catecholamine support which may have detrimental effects, particularly in patients with ischemic myocardium [47]

Acid base and electrolyte abnormalities Metabolic acidosis occurs infrequently following extracorporeal circulatory support with the currently used pump oxygenator systems and priming techniques When metabolic acidosis is present postoperatively it may reflect inadequate perfusion during bypass particularly if the period of bypass was prolonged More commonly, metabolic acidosis results from low cardiac output postoperatively with poor tissue perfusion Since metabolic acidosis may adversely effect myocardial function [62] it should be treated vigorously Improvement in cardiac output is obviously an important aspect of therapy Vasopressor agents may be more effective in the treatment of low cardiac output if the acidosis is corrected [63] Arterial hypoxemia if present should also be corrected to assure adequate oxygen delivery to the tissues.

postoperatively either spontaneously or surgically induced it is usually transient but should be treated by ventricular pacing if the ventricular rate is slow A normally conducted rhythm usually ensues although occasionally permanent pacing is required If serious atrioventricular conduction abnormalities are present preoperatively or occur intraoperatively we place permanent as well as temporary epicardial electrodes on the right or left ventricular surface at the time of the cardiac procedure The permanent electrodes are implanted in the subcutaneous layer of the anterior abdominal wall If conduction disturbances persist in these patients early postoperatively they are managed by the temporary wires If use of a permanent pacer becomes necessary a pulse generator can be connected to the implanted electrodes as a secondary procedure

Systematic detection and treatment of impaired cardiac performance Based on the above information we currently employ in our cardiac surgical intensive care unit a systematic approach to the detection and treatment of impaired cardiac performance As noted previously appropriate selection of patients for operation and precise and proper conduct of the operative procedure are the most important factors preventing or minimizing the occurrence of impaired cardiac function in the postoperative period

Clinical evidence for low cardiac output may be present in some patients If the usual clinical signs are not present however one may have a high index of suspicion that it is low if arterial hypotension high left atrial pressure poor peripheral perfusion and metabolic acidosis are present If low cardiac output is present preoperatively the likelihood that it will be present postoperatively is high Provisions should be made to measure cardiac output postoperatively in all the above types of patients Correctable factors contributing to low cardiac output such as residual cardiac defects excessive bleeding with cardiac tamponade and acid base and electrolyte abnormalities should be systematically sought and treated (Table III) If the heart rate is less than 80 to 90 per minute cardiac output may be augmented by increasing the rate to 90 to 110 per minute with appropriate atrial or ventricular pacing If the heart rate is rapid (greater than 130 to 140 per minute) the type of tachycardia should be accurately identified and treated

Table III Mechanisms to improve cardiac performance following cardiac operations

1	Correction of residual cardiac abnormalities
2	Control of bleeding disorders and relief of cardiac tamponade
3	Correction of acid base and electrolyte disturbances
4	Optimization of cardiac rate and rhythm
5	Optimization of left ventricular preload and afterload
6	Improvement in myocardial contractility

Once these abnormalities have been identified and the appropriate measures taken to correct them cardiac output should be remeasured if it is still low interventions to directly improve myocardial performance are indicated (Table IV) We believe that cardiac output mean aortic pressure and left atrial pressure are the most useful parameters to assess cardiac function following operation

Cardiac index less than 2 0 L/min/m² As noted above a cardiac index of less than 2 0 L/min/M early postoperatively is associated with high morbidity and mortality rates If cardiac index is below this level and the mean left atrial pressure is 14 mm Hg or less blood should be infused to augment left ventricular filling pressure and volume and increase cardiac output If the hemoglobin level is greater than 16 Gm per 100 ml albumin rather than whole blood should be used Volume is administered under these circumstances regardless of the level of mean arterial pressure On occasion if the arterial pressure is high with evidence of significant peripheral vasocontriction trimethaphan or sodium nitroprusside may be administered concomitantly to reduce arterial pressure particularly if bleeding is a potential problem As noted in Fig o however this may depress cardiac output further and additional volume infusion may be required

If the mean left atrial pressure is between 15 and 18 mm Hg and the mean arterial pressure is less than 100 mm Hg epinephrine should be administered If the mean arterial pressure is greater than 100 mm Hg dopamine or isoproterenol may be used unless the heart rate is greater than 120 per minute or if there is ventricular irritability in which case epinephrine is used If the mean left atrial pressure is greater than 18 mm Hg and the arterial pressure is less than 100

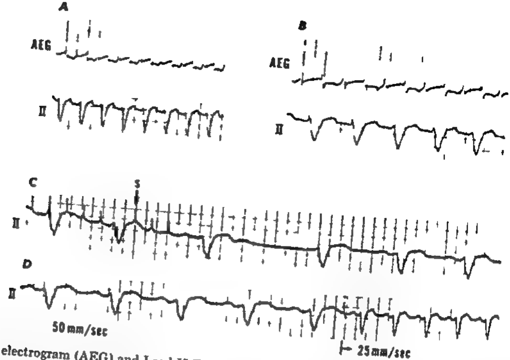

Fig 8 Atrial electrogram (AEG) and Lead II ECG in a patient with atrial flutter at about 300 beats per minute and 2 1 A V conduction Panel *A* shows tracings at 25 mm /sec and Panel *B* at 50 mm /sec The atria were paced at 370 beats/min for 30 seconds (Panel *C*) With abrupt cessation of atrial pacing (*S* = stimulus artifact) regular sinus rhythm ensued (Panel *D*) The diagnosis of atrial flutter could not be made from standard 12 lead ECGs in this patient (From Waldo A L MacLean W A H and James T N Utilization of the cardiac catheterization laboratory for the diagnosis and treatment of cardiac arrhythmias and conduction disturbances, Ala J Med Sci 11 120 1974 Reproduced by permission of Dr A L Waldo and the Alabama Journal of the Medical Sciences)

vagal tone (carotid massage infusion of neostigmine or elevation of systolic blood pressure with vasopressor agents such as methoxamine [Vasoxyl] or phenylephrine hydrochloride [Neosynephrine]) Atrial pacing at a faster rate than the spontaneous rate of paroxysmal atrial tachycardia can capture the atria and interrupt the arrhythmia

ATRIAL FLUTTER This generally results in an atrial rate of 280 to 320 beats per minute and the ventricular response is most often a fixed ratio of the atrial rate (i e 2 1 or 4 1) Pacing the atria at a faster rate is occasionally successful in interrupting this arrhythmia and restoring sinus rhythm (Fig 8) Most often the flutter is converted to atrial fibrillation by overdrive pacing and this rhythm is then relatively easy to control with digitalis [69] If the ventricular rate with atrial fibrillation is slow it can be best controlled by ventricular pacing, particularly in the presence of ventricular extrasystoles In addition to suppressing the ectopic beats, pacing under these conditions will improve cardiac output [70]

Junctional arrhythmias If a junctional tachycardia is present digitalis is contraindicated since it may further enhance the automaticity of the junctional pacemaker Intravenous lidocaine (Xylocaine) is the drug of choice under circumstances since it suppresses the automaticity of the junctional pacemaker without significant effects on myocardial contractility or atrioventricular conduction If the tachycardia is significantly impairing cardiac function with resulting hypotension paired ventricular pacing to effectively halve the rate may occasionally be effective Junctional arrhythmias resulting in bradycardia can be effectively treated by atrial or ventricular pacing which often increases cardiac output [71]

Ventricular arrhythmias Ventricular extrasystoles may be treated by pacing the ventricles at a slightly higher rate than the intrinsic ventricular rate either atrially or ventricularly to suppress the ectopic foci When this is not successful or the ventricular rate is already rapid, use of lidocaine or procainamide (Pronestyl) is generally effective

Ventricular tachycardia can occasionally be treated by pacing but generally cardioversion combined with appropriate drug therapy (lidocaine or procainamide) is necessary If hypokalemia is present, it should be treated with intravenous potassium chloride

Atrioventricular dissociation If this occurs

o, > 110 mm Hg) on 40 per cent inspired)gen concentration (2) cardiac performance is d,ed satisfactory and adequate to sustain the work of breathing which would be pected after extubation (3) cardiac arrhyth are absent or under control (4) reoperation r bleeding will not be required

In our unit the type of respiratory support used r adults differs from that used in babies and ung children In adults ventilation is controlled ith a volume ventilator (Drager) or is controlled assisted with a pressure cycled ventilator ird) Ventilation is maintained in patients who ve no severe cardiac or pulmonary dysfunction r a period of about 4 to 12 hours Generally four terial blood gas analyses are obtained one ortly after the patient is brought from the erating room the second approximately 6 ours later and the third shortly before antic ated extubation A subsequent blood gas anal is done 30 minutes after extubation

There are certain specific considerations which pply to adult patients on controlled intermit nt positive pressure ventilation A frequency of etween 9 and 14 breaths per minute is generally atisfactory For the average adult patient tidal olumes range between 600 and 900 ml It appears hat there are chest wall reflexes which produce a eeling of dyspnea in patients who have adequate rterial oxygen saturation but low tidal volumes ncreasing the tidal volume often obviates the eeling of breathlessness This coincides with an rterial P_{CO_2} of between 28 and 34 mm Hg and roduces a moderate alkalemia Muscle relaxants nd paralyzing agents are not generally used and norphine in small doses is used to control pain nd restlessness and allow adequate control of entilation. The fraction of inspired oxygen ($F_{I_{O_2}}$) s generally adjusted to 40 per cent If there is a large alveolar arterial oxygen gradient with resulting arterial oxygen tensions of less than 110 mm. Hg the $F_{I_{O_2}}$ is increased In addition most cases of postoperative hypoxemia will respond to continuous positive pressure ventilation with 5 to 10 mm Hg of positive end expiratory pressure (PEEP) This does not adversely affect cardiac output in most cases We prefer a volume controlled ventilator because $F_{I_{O_2}}$ can be adjusted to any level although in many patients a pressure-cycled ventilator would be equally satisfactory In patients with significant pulmonary dysfunction volume control is the more satisfactory mode since disturbances of pulmonary mechanics can be more readily corrected

Infants and children under 8 years of age are managed with a nasotracheal tube and controlled ventilation (Bournes ventilator for infants and children less than 1 years and the Drager for older children) When cardiac performance and arterial blood gas measurements are judged satisfactory the older children are extubated Infants and smaller children are first transferred to a continuous positive airway pressure breathing system (CPAP)[3] The $F_{I_{O_2}}$ is tapered from 70 to 40 per cent followed by a decrease in the continuous positive airway pressure from 6 to 0 mm Hg. If arterial P_{O_2} remains above 80 mm Hg and P_{CO_2} below 55 mm Hg they are then extubated

Special measures Laryngeal and tracheal injury secondary to airway intubation has received increased attention in recent years[10] Injury to the vocal cords the subglottic larnyx and the trachea is primarily attributable to pressure phenomena (i.e inflation of the balloon cuff angulation of the tracheostomy or endotracheal tube impingement of the tip of the tube on the wall of the trachea and movement of the tip of the tube) Laryngotracheal injury usually occurs in three groups of patients (1) those who require prolonged ventilatory support (2) those with low cardiac output or shock and (3) infants and children Presently we prefer Portex rather than rubber endotracheal tubes In children an effort is made to keep the tube loosely fitting in the trachea The tubes are securely fixed at the lips or the nares and motion against the firm arm of the ventilator is avoided thus preventing a rocking action at the tip of the endotracheal tube Inspired gas is at all times humidified and suctioning on the endotracheal tube is performed as necessary by the nursing staff Tracheostomies are avoided in infants and children and are infrequently done in adults With these techniques, the incidence of laryngeal and tracheal stenosis has been significantly reduced

In patients with moderate pulmonary dysfunction and excessive tracheal bronchial secretions following extubation chest physiotherapy is quite important Peroral or nasotracheal aspiration is utilized infrequently since arterial oxygen desaturation and vasovagal reflexes can be produced with this maneuver Bronchoscopy is also used infrequently

Prolonged ventilatory support is generally

Table IV Logic for analysis and treatment of impaired cardiac performance early after operation

Mean left atrial pressure (mm. Hg)	*Mean arterial pressure (mm. Hg)*	*Cardiac index (L./min./M.²)*		
		Under 2.0	*2.0-3.0*	*Over 3.0*
7 or less		Blood	Blood*	Blood
7-14		Blood*	Blood*	—
15-18	Under 100	Epinephrine	—	—
	Over 100	Epinephrine, dopamine† or Isuprel†	Trimethaphan or nitroprusside‡	—
Above 18	Under 100	Epinephrine, dopamine† or Isuprel†	—	—
	Over 100	Epinephrine, dopamine† or Isuprel† *plus* trimethaphan or nitroprusside	Trimethaphan or nitroprusside‡	—

*Use albumin if hemoglobin concentration is > 16 Gm. per 100 ml.
†If frequent premature contractions are present or heart rate is above 120 per minute, use epinephrine.
‡Optional in this category.

mm. Hg, epinephrine, dopamine, or isoproterenol should be infused. If the mean arterial pressure is greater than 100 mm. Hg, trimethaphan or nitroprusside is infused to reduce arterial pressure and left ventricular afterload. Epinephrine, dopamine, or isoproterenol is infused concomitantly to improve myocardial contractility. Cardiac index should be measured at intervals during the period these interventions are employed to assess the response to therapy. If, following this treatment program, cardiac performance does not improve or further deteriorates, institution of intra-aortic balloon pumping should be considered, using the criteria previously outlined.

Cardiac index between 2.0 and 3.0 L./min./M.² If the mean left atrial pressure is less than 14 mm. Hg, blood or albumin should be infused to achieve a ventricular filling pressure which is optimal (12 to 14 mm. Hg). Other interventions are generally not necessary unless the mean arterial pressure is over 100 mm. Hg and the left atrial pressure is above 15 mm. Hg. Under these conditions trimethaphan or nitroprusside may be infused to reduce arterial pressure and ventricular afterload.

Cardiac index over 3.0 L./min./M.² Under these conditions no therapy is indicated except that blood can be infused if left atrial pressure is less than 7 mm. Hg. This again insures optimal left ventricular filling pressure.

Although not always successful, the above logic has resulted in a more precise analysis of impaired cardiac performance after cardiac surgical procedures than previously utilized methods, and has provided a systematic plan of treatment which alters left ventricular filling pressure (preload), impedance to ejection (afterload), and contractility. This logic is based primarily upon data accumulated in adult patients, although information on cardiac performance in infants and children has recently become available.[1, 3, 4] With the acquisition of additional information and the perfection of techniques for automated infusion of various pharmacologic agents, it may be possible to set and automatically maintain optimal levels for left atrial and arterial pressure and heart rate and, thereby, achieve optimal cardiac performance.

Pulmonary system

Management of the pulmonary system postoperatively requires the following: (1) adequate alveolar ventilation, usually attained with the use of mechanical ventilators; (2) satisfactory matching of ventilation and perfusion, making adjustments based on knowledge of the effects on pulmonary performance of low cardiac output, diffusion problems, elevated pulmonary vascular resistance, and the presence of atelectasis; (3) satisfactory oxygen delivery, based on adequate red cell function, hemoglobin concentration, and cardiac output, and knowledge of the metabolic requirements; and (4) periodic evaluation of the adequacy of pulmonary function by arterial blood gas measurements.

After open intracardiac operations, most patients are kept intubated and ventilated for a period of time. Generally, the patient is ventilated until the following criteria are fulfilled: (1) there is satisfactory alveolar ventilation as indicated by acceptable arterial carbon dioxide tension ($Pco_2 < 55$ mm. Hg) and absence of hypoxemia

deficits or behavioral changes the signs and symptoms improve or disappear in many patients in the postoperative period Thus even though there may be a severe neurologic deficit initially careful attention to the hemodynamic state of the patient and to supportive measures may lead to satisfactory and often complete neurologic recovery late after operation

Behavioral changes may manifest themselves early after operation or in the later postoperative period These include changes in affect periods of confusion or disorientation and frank delirium Many patients complain of insomnia A number of patients develop signs of depression and children may frequently have nightmares Most of these changes are benign and self limited Treatment consists of optimal nursing care reassurance of the patient and his family and active involvement of the family in the care of the patient Neurologic deficits should be treated aggressively by the physician and physiotherapist The knowledge that many of these neurologic deficits improve should cause all concerned to maintain an optimistic outlook and to manage these patients aggressively

REFERENCES

1. Kirklin, J W Systems analysis in surgical patients (The Martwen Memorial Lectures 1u) Glasgow 19 0 University of Glasgow
2. Kirklin, J W and Rastelli, G C Low cardiac output after open heart intracardiac operations Prog Cardio vasc Dis 10 117 1967
3. Dietzman R H Ersek R A Lillehei C W Castaneda A R and Lillehei R A Low output syndrome Recognition and treatment J Thorac Cardiovasc Surg 57 138, 1969
4. Parr C V S Blackstone E H and Kirklin J W Cardiac performance and mortality early after intracardiac surgery in infants and young children Circulation 51 867 19 5
5. Appelbaum, A Kouchoukos N T Blackstone F H and Kirklin, J W The early risks of open mitral valve surgery Am J Cardiol. 37 01 19,6
6. Barratt Boyes, B C and Wood E H Cardiac output and related measurements and pressure values in the right heart and associated vessels together with an analysis of the hemodynamic response to the inhalation of high oxygen mixtures in healthy subjects J Lab Clin Med 51 2, 1958
7. Bassingthwaighte, J B Sturm R E and Wood E H Advances in indicator dilution techniques applicable to studies of the acutely ill patient Mayo Clin Proc 45 563 1970
8. Parr G V S Kirklin, J W Pacifico A D Blackstone E H., and Laundsen P Cardiac performance in infants after repair of total anomalous pulmonary venous connection, Ann Thorac Surg 17 561 19 4
9. Sekelj, P Tait, G R and Nathanson M M Studies on dye dilution curves using a digital computer IEEE Trans. Biomed Eng 13 32 1966
10. Forrester J S Ganz W Diamond G McHugh T., Chonette D W and Swan H J C Thermodilution cardiac output determination with a single flow-directed catheter Am Heart J 83 306 1972
11. Kouchoukos, N T., Sheppard L C McDonald D A., and Kirklin J W Estimation of stroke volume from the central arterial pressure contour in postoperative patients, Surg Forum 20 180 1969
12. Kouchoukos N T Sheppard L C and Kirklin J W Automated patient care following cardiac surgery in editor Brest, A N., Cardiovascular clinics, Vol 3, No 3 Philadelphia, 1971 F A Davis Company p 109
13. A review of the patient monitoring system at the University of Alabama Medical Center Arthur D Little Inc., Cambridge Mass. 02140 Appendix C March 1973
14. Kloster F E Bristow J D Starr A McCord C., and Griswold H E. Serial cardiac output and blood volume studies following cardiac valve replacement Circulation 33 .8 1966
15. Rastelli G C and Kirklin J W Hemodynamic state early after prosthetic replacement of mitral valve Circulation 34 448 1966
16. Forrester J., Diamond G Ganz, W Danzig R and Swan H J C Right and left heart pressures in the acutely ill patient, Clin Res. 18 306 1970
17. Kirklin J W and Theye, R A. Cardiac performance after open intracardiac surgery Circulation 28 1061 196.
18. Reid, D J Digerness, S B and Kirklin J W Changes in whole body venous tone and distribution of blood after open intracardiac surgery Am J Cardiol. 22 621 1968
19. Kouchoukos, N T Kirklin J W., Sheppard L C and Roe, P Effect of elevation of left atrial pressure by blood infusion on stroke volume early after cardiac operations, Surg Forum 22 126 1971
20. Riley S M Jr Blackstone E H and Kouchoukos N T Left ventricular diastolic pressure volume relations in patients with mitral valvular disease Surg Forum 26 220 1975
21. Crexells, C Chatterjee K. Forrester J S Dikshit K., and Swan H. J C Optimal level of filling pressure in the left side of the heart in acute myocardial infarction N Engl J Med. 289 1.63 1973
22. Gomes, M M R and McGoon D C Bleeding patterns after open heart surgery J Thorac Cardiovasc Surg 60 87 1970
23. Hill J D Johnson D C Miller C E Jr Kerth W J and Gerbode F Latent mediastinal tamponade after open heart surgery Arch Surg 99 808 1969
24. Wisch, N Litwak R S Lukban S B., and Glass J L Hematologic complications of open heart surgery Am J Cardiol 31 282, 1973
25. Allen, W B Karp R B and Kouchoukos N T Mitral valve replacement Starr Edwards cloth covered composite-seat prosthesis, Arch Surg 109 642 1974
26. Stephenson L. W., Kouchoukos N T Kirklin J W Karp R B and Pacifico A D Combined aortic and mitral valve replacement Results in .51 patients Circulation 51 and 52 (Suppl. II) II 31 1975
27. Kouchoukos, N T and Stephenson L W Indications for and results of tricuspid valve replacement in Advances in Cardiology New York, S Karger A G (in press)
28. Gault J H Covell J W Braunwald E., and Ross J Jr Left ventricular performance following correction of free aortic regurgitation Circulation 42 773 1970
29. Hildner F J Javier R P Cohen L A., Samet, P

required when there is low cardiac output postoperatively Airway care, avoidance of high F_{IO} and use of diuretics are especially important in these seriously ill patients in addition to measures to improve cardiac function Respiratory support can be discontinued only when cardiac output has increased to levels adequate to sustain the work of breathing in addition to the metabolic demands of other systems Weaning from mechanical ventilators under these circumstances should be based on both blood gas analysis and direct or indirect analysis of cardiac performance

Renal system

With the currently utilized techniques of extracorporeal circulatory support employing moderate or severe hemodilution, acute tubular necrosis and renal failure are infrequent complications following cardiac operations The majority of patients in whom these complications develop usually have significant impairment of cardiac and renal function preoperatively and often have evidence of low cardiac output postoperatively Renal dysfunction as evidenced by elevated blood urea nitrogen and creatinine levels has been observed in 29 per cent of a series of 507 adult patients following open cardiac surgical procedures and was associated with a mortality rate of 30 per cent [75] Cardiac failure sepsis and pulmonary insufficiency are often associated with renal dysfunction, and appropriate measures should be taken to correct these complications when they occur

In patients undergoing open cardiac operations with extracorporeal circulatory support urine flow decreases progressively during induction of anesthesia and thoracotomy Anuria is generally present during the early period of cardiopulmonary bypass even when hemodilution of the perfusate is employed During the first few hours after operation, urine output is high in patients in whom hemodilution is used [76] This is probably related to the osmotic diuretic effects of the glucose or mannitol used in the perfusate Urine output then declines to more normal levels (30 to 50 ml per hour) High urine flow rates produced by osmotic diuresis have been shown experimentally to prevent pathologic renal tubular changes that occur following extracorporeal circulatory support associated with low urine flow [77]

If low urine output occurs following operation low cardiac output may be present, and appropriate measures should be taken to detect and treat it as outlined in the previous section If urine output continues to be low (less than 15 ml per hour for two consecutive hours), additional therapy is indicated If the mean left atrial pressure is less than 15 mm Hg, 25 Gm of mannitol may be infused over a 1 hour period This dosage can be repeated after 3 to 4 hours if the urine output remains low If the mean left atrial pressure is greater than 15 mm Hg 20 to 40 mg of furosemide (Lasix) should be given intravenously This drug produces a marked diuresis but may increase urinary potassium losses Serum potassium concentrations should thus be monitored closely when it is used In addition to its diuretic effect furosemide can reduce left ventricular filling pressure in patients with chronic heart failure either by vasodilatation in the pulmonary vasculature increase in peripheral venous pooling, or both These effects occur before the onset of significant diuresis [78] With the use of hemodilution and diuretic therapy as outlined postoperative renal failure in the absence of severe cardiac failure and low cardiac output has been encountered infrequently in our experience Hemodialysis is occasionally required postoperatively although survival in a recently reported series of 31 patients following major cardiovascular surgical procedures was only 26 per cent [9]

Central nervous system

Central nervous system dysfunction following extracorporeal circulatory support is usually manifested as diffuse or localized neurologic deficits or as behavioral abnormalities Air embolization is an important cause of neurologic dysfunction following operation Prevention or minimization of air embolization is based on rigorous adherence to a routine protocol for venting the heart during operation and for evacuation of air from the cardiac chambers when cardiopulmonary bypass is discontinued Embolization of particulate matter such as calcium, fat, microaggregates and fibrin may also cause neurologic injury The use of arterial filters and of oxygenators which contain filters in the extracorporeal circuit has reduced the incidence of embolization of particulate matter and presumably of postoperative neurologic deficits [80]

Whatever the cause of the neurologic dysfunction and whether it results in specific neurologi

ficits or behavioral changes the signs and symptoms improve or disappear in many patients in the postoperative period Thus even though there may be a severe neurologic deficit initially careful attention to the hemodynamic state of the patient and to supportive measures may lead to satisfactory and often complete neurologic recovery late after operation

Behavioral changes may manifest themselves early after operation or in the later postoperative period These include changes in affect periods of confusion or disorientation and frank delirium Many patients complain of insomnia A number of patients develop signs of depression and children may frequently have nightmares Most of these changes are benign and self limited Treatment consists of optimal nursing care reassurance of the patient and his family and active involvement of the family in the care of the patient Neurologic deficits should be treated aggressively by the physician and physiotherapist The knowledge that many of these neurologic deficits improve should cause all concerned to maintain an optimistic outlook and to manage these patients aggressively

REFERENCES

1 Kirklin, J W Systems analysis in surgical patients (The Macewen Memorial Lectures 15) Glasgow 19 0 University of Glasgow
2 Kirklin, J W and Rastelli, G C Low cardiac output after open heart intracardiac operations Prog Cardiovasc Dis. 10 117 1967
3 Dietzman R H Ersek R A Lillehei C W Castaneda A R and Lillehei R A Low output syndrome Recognition and treatment J Thorac Cardiovasc Surg 57 138 1969
4 Parr G V S Blackstone E H and Kirklin J W Cardiac performance and mortality early after intracardiac surgery in infants and young children Circulation 51 867 1975
5 Appelbaum A Kouchoukos N T Blackstone E H and Kirklin J W The early risks of open mitral valve surgery Am J Cardiol 37 201 19 6
6 Barratt Boyes B G and Wood E H Cardiac output and related measurements and pressure values in the right heart and associated vessels together with an analysis of the hemodynamic response to the inhalation of high oxygen mixtures in healthy subjects J Lab Clin Med. 51 72 1958
7 Bassingthwaighte J B Sturm R E and Wood E H Advances in indicator dilution techniques applicable to studies of the acutely ill patient Mayo Clin Proc 45 63 19 0
8 Parr G V S Kirklin J W Pacifico A D Blackstone E H and Launidsen ? Cardiac performance in infants after repair of total anomalous pulmonary venous connection, Ann Thorac Surg 17 561 1974
9 Sekelj P Tait, G R and Nathanson M H Studies on dye dilution curves using a digital computer IEEE Trans Biomed Eng 13 3? 1966
10 Forrester J S Ganz W Diamond G McHugh T Chonette D W and Swan H J C Thermodilution cardiac output determination with a single flow directed catheter Am Heart J 83 306 1972
11 Kouchoukos, N T., Sheppard L C McDonald D A., and Kirklin J W Estimation of stroke volume from the central arterial pressure contour in postoperative patients Surg Forum 20 180 1969
12 Kouchoukos N T Sheppard L C and K? ? J W Automated patient care following cardiac surgery in editor Brest A N Cardiovascular clinics Vol 3 No 3 Philadelphia 1971 F A Davis Company p 109
13 A review of the patient monitoring system at the University of Alabama Medical Center Arthur D Little Inc Cambridge Mass 02140 Appendix C March 1973
14 Kloster F E Bristow J D Starr A McCord C., and Griswold H E Serial cardiac output and blood volume studies following cardiac valve replacement Circulation 33 528 1966
15 Rastelli, G C and Kirklin J W Hemodynamic state early after prosthetic replacement of mitral valve Circulation 34 448 1966
16 Forrester J Diamond G Ganz W Danzig R and Swan H J C Right and left heart pressures in the acutely ill patient Clin Res. 18 306 1970
17 Kirklin J W and Theye R A Cardiac performance after open intracardiac surgery Circulation 28 1061 1963
18 Reid D J Digerness S B and Kirklin J W Changes in whole body venous tone and distribution of blood after open intracardiac surgery Am J Cardiol 22 621 1968
19 Kouchoukos N T Kirklin J W Sheppard L C and Roe P Effect of elevation of left atrial pressure by blood infusion on stroke volume early after cardiac operations Surg Forum 22 126 1971
20 Riley S M Jr Blackstone E H and Kouchoukos N T Left ventricular diastolic pressure volume relations in patients with mitral valvular disease Surg Forum 26 220 1975
21 Crexells, C Chatterjee K Forrester J S Dikshit K and Swan H J C Optimal level of filling pressure in the left side of the heart in acute myocardial infarction N Engl J Med 289 1263 1973
22 Gomes M M R and McGoon D C Bleeding patterns after open Heart surgery J Thorac Cardiovasc Surg 60 87 1970
23 Hill J D Johnson D C Miller G E Jr Kerth W J and Gerbode F Latent mediastinal tamponade after open heart surgery Arch Surg 99 808 1969
24 Wisch N Litwak R S Lukban S B and Glass J L Hematologic complications of open heart surgery Am J Cardiol. 31 282 1973
25 Allen W B Karp R B and Kouchoukos N T Mitral valve replacement Starr Edwards cloth covered composite-seat prosthesis Arch Surg 109 642 1974
26 Stephenson L W Kouchoukos N T Kirklin J W Karp R B and Pacifico A D Combined aortic and mitral valve replacement Results in 251 patients Circulation 51 and 52 (Suppl. II) II 31 1975
27 Kouchoukos N T and Stephenson L W Indications for and results of tricuspid valve replacement in Advances in Cardiology New York S Karger A C (in press)
28 Gault J H Covell J W Braunwald E and Ross J Jr Left ventricular performance following correction of free aortic regurgitation Circulation 42 773 1970
29 Hildner F J Javier R P Cohen L A Samet, P

29. Nathan M J Yahr W Z and Greenberg J J Myocardial dysfunction associated with valvular heart disease Am J Cardiol 30 319 1972
30. Spencer F C Green G E Tice D A Wallsh E Mills N L and Glassman E Coronary artery bypass grafts for congestive heart failure A report of experience with 40 patients J Thorac Cardiovasc Surg 62 529 1971
31. Kouchoukos N T Doty D B Buettner L E and Kirklin J W Treatment of postinfarction cardiac failure by myocardial excision and revascularization Circulation 35 36 (Suppl I) 72 1972
32. Kouchoukos N T Kirklin J W and Oberman A An appraisal of coronary bypass grafting Sixth Annual George C Griffith Lecture Circulation 50 11 1974
33. Lapin E S Murray J A Bruce R A and Winterscheid L Changes in maximal exercise performance in the evaluation of saphenous vein bypass surgery Circulation 47 1164 1973
34. Taber R E Morales A R and Fine C Myocardial necrosis and the postoperative low cardiac output syndrome Ann Thorac Surg 4 12 1967
35. Najafi H Henson D Dye W S Javid H Hunter J A Callaghan R Eisenstein R and Julian O C Left ventricular hemorrhagic necrosis Ann Thorac Surg 7 550 1969
36. Buckberg G D Towers B Paglia D E Mulder D G and Maloney J Subendocardial ischemia after cardiopulmonary bypass J Thorac Cardiovasc Surg 64 669 1972
37. Goldschlager N Gerbode F Osborn J J and Cohn K E Patterns of myocardial oxygen and lactate extraction in patients undergoing cardiopulmonary bypass Am Heart J 83 167 1972
38. Oldham H N Jr Roe C R Young W G Dixon S H Jr and Sabiston D C Jr Intraoperative detection of myocardial damage during coronary artery surgery by plasma creatinine phosphokinase isoenzyme analysis Surgery 74 917 1973
39. Sapsford R N Blackstone E H Kirklin J W Karp R B Kouchoukos N T Pacifico A D Roe C R and Bradley E L Coronary perfusion versus cold ischemic arrest during aortic valve surgery Circulation 44 1190 1974
40. Cooley D A Reul G J and Wukasch D C Ischemic contraction of the heart Stone heart Am J Cardiol 29 575 1972
41. Wukasch D C Reul C L Milam J D Hallman G L and Cooley D A The stone heart syndrome Surgery 72 1071 1972
42. Goldfarb D and Bahnson H T Early and late effects on the heart of small amounts of air in the coronary circulation J Thorac Cardiovasc Surg 46 368 1963
43. Levine F H and Copeland J G Prosthetic replacement of the mitral valve Continuing assessment of the 100 patients operated upon during 1961 1965 Circulation 47 518 1973
44. Linhart J W and Wheat M W Jr Myocardial dysfunction following aortic valve replacement The significance of coronary artery disease J Thorac Cardiovasc Surg 54 259 1967
45. Coleman E H and Soloff L A Incidence of significant coronary artery disease in rheumatic valvular heart disease Am J Cardiol 25 401 1970
46. Cartmill T B DuShane J W McGoon D C and Kirklin J W Results of repair of ventricular septal defect J Thorac Cardiovasc Surg 52 486 1966
47. Mueller H Giannelli S Jr Ayres S M Conklin E F and Gregory J J Effect of isoproterenol on ventricular work and myocardial metabolism in the postoperative heart Circulation 37 (Suppl II) 1968
48. Coffin L H Ankeney J L and Beheler E M Experimental study and clinical use of epinephrine for treatment of low cardiac output syndrome, Circulation 33 (Suppl I) 78 1966
49. Fordham R M M and Resnekov L Comparison of hemodynamic effect of intravenous isoprenaline and adrenaline after aortic valvular homograft replacement Br Heart J 32 393 1970
50. Holzer J Karliner J S O Rourke R A Pitt W and Ross J R Jr Effectiveness of dopamine in patients with cardiogenic shock Am J Cardiol 32 79 1973
51. Holloway E L Stinson E B Derby G C and Harrison D C Action of drugs in patients early after cardiac surgery I Comparison of isoproterenol and dopamine Am J Cardiol 35 656 1975
52. Viljoen J F Estafanous F G and Kellner G A Propranolol and cardiac surgery J Thorac Cardiovasc Surg 64 826 1972
53. Olson H G Miller R R Amsterdam E A Wood M Brocchini R and Mason D T The propranolol withdrawal rebound phenomenon Acute and catastrophic exacerbation of symptoms and death following the abrupt cessation of large doses of propranolol in coronary artery disease Am J Cardiol 35 162 1975 (abst)
54. Ross J Jr and Braunwald E The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin Circulation 29 739 1964
55. Kouchoukos N T Sheppard L C and Kirklin J W Effect of alterations in arterial pressure on cardiac performance early after open intracardiac operations J Thorac Cardiovasc Surg 64 563 1972
56. Appelbaum A Blackstone E H Kouchoukos N T and Kirklin J W Effect of afterload reduction on cardiac output in infants after intracardiac surgery Circulation 51 and 52 (Suppl II) II 151 1975
57. Hirshorn S and Kaiser G A The effect of changes in left ventricular end diastolic pressure on the distribution of coronary blood flow and on the electrical activity of the heart in Skinner D B and Ebert P A editors Current Topics in Surgical Research Vol 2 New York 1970 Academic Press Inc p 463
58. Buckberg G D Archie J P Fixler D E and Hoffman J I E Experimental subendocardial ischemia during left ventricular hypertension Surg Forum 22 124 1971
59. Buckley M J Graver J M Gold H K Mundth E D Daggett W M and Austen W G Intra-aortic balloon pump assist for cardiogenic shock after cardiopulmonary bypass Circulation 47 48 (Suppl III) 1973
60. Parker F B Neville J F Hanson E L and W R Intraaortic balloon counterpulsation and cardiac surgery Ann Thorac Surg 17 144 1974
61. Lamberti J J Cohn L H Lesch M and Collins J J Jr Intra aortic balloon counterpulsation Indications and long term results in postoperative left ventricular power failure Arch Surg 109 766 1974
62. Darby T D Aldinger E E Gadsden R H and Thrower W B Effects of metabolic acidosis on ventricular isometric systolic tension and the response to epinephrine and levarterenol Circ Res 8 1242 1960
63. Cook W A Webb W R and Unal M O Myocardial function capacity in response to compensated and uncompensated respiratory alkalosis Surg Forum 16 186 1965
64. Flemma R J and Young W G The metabolic effe

of mechanical ventilation and respiratory alkalosis in postoperative patients Surgery 56 36 1964
Harris, P D Malm J R Bowman F O Jr Hoffman B F Kaiser G A and Singer D A Epicardial pacing to control arrhythmias following cardiac surgery Circulation 37 38 (Suppl. II) 1 8 1968
Waldo A. L Ross, [redacted] and Kaiser G A The epicardial electrogram in the diagnosis of cardiac arrhythmias following cardiac surgery Geriatrics 26 108 1971
Buckberg G D Fixler D E Archie J P and Hoffman, J I E Experimental subendocardial ischemia in dogs with normal coronary arteries Circ Res 30 67 1972
Waldo A. L. and Kaiser G A Electrophysiological considerations for the cardiac surgical patient *in* Litwak R S and Juanado R editors Preoperative operative and postoperative care of the cardiac surgical patient New York, 1976 Intercontinental Medical Book Corporation
Waldo A. L., MacLean W A H Karp R [redacted] Kouchoukos, N T and James, T N Sustained rapid atrial pacing to control supraventricular tachycardias following open heart surgery Circulation 51 and 52(Suppl II) II 13, 19 5.
Litwak R. S Kuhn L A Gadboys H L Lukban S J and Sakurai, H Support of myocardial performance after open cardiac operations by rate augmentation J Thorac Cardiovasc. Surg 56 484 1968
Friesen W G Woodson R D Ames A W Herr R H Starr A., and Kassebaum D G A hemodynamic comparison of atrial and ventricular pacing in postoperative cardiac surgical patients, J Thorac Cardiovasc Surg. 55 771 1968
72. Nictona M [redacted] Stevens, P M., Viroglov J and Alvarez A A *Physiologic evaluation of positive end expiratory* pressure ventilation Chest 64 10 1973
73 Stewart S III Edmunds, L. H., Jr Kirklin J W., and Allarde R. R Spontaneous breathing with continuous positive airway pressure after open intracardiac operations [redacted] infants J Thorac Cardiovasc Surg 65 37 1973
74 Geffin B Grillo H C Cooper J D and Pontoppidan H Stenosis following tracheostomy for respiratory care *J A M A 216 1984 1971*
75 Abel R. M. Wick, J Beck, C H Jr., Buckley M J., and Austen W G Renal dysfunction following open heart operations, Arch Surg. 108 175 1974
76 Mielke J E Hunt J C Maher F T and Kirklin J W Renal performance during clinical cardiopulmonary bypass with and without hemodilution J Thorac Cardiovasc. Surg. 51 229 1966
77 Schuster S R. Rakvan [redacted] Vawter [redacted] F and Narter *N An experimental study of the effect of mannitol* during cardiopulmonary bypass, Circulation 29 (Suppl I) 72, 1964
78 Dikshit, K Vyden J K Forrester J S Chatterjee K Prakash, R and Swan H J C Renal and extrarenal hemodynamic effects of furosemide in congestive failure after acute myocardial infarction N Engl. J Med. 288 1087 1973.
79 Casali R Simmons R L. Najarian J S von Hartitzsch, B Buselmeier T J and Kjellstrand C M Acute renal insufficiency complicating major cardiovascular surgery Ann Surg 181 3 0 19 5
80 Aguilar M J Gerbode F and Hill, J D Neuropathologic complications of cardiac surgery J Thorac Cardiovasc Surg 61 6 6 1971

Appraisal and reappraisal of cardiac therapy

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Cardiac effects of disopyramide

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In 1962 Mokler and Van Arman[1] reported a study of the antiarrhythmic effects of disopyramide (Norpace Rhythmodan) They showed that disopyramide was efficacious in the treatment of experimental atrial arrhythmias induced electrically or by application of aconitine and ventricular arrhythmias induced by ouabain or by a Harris two stage coronary ligation Antiarrhythmic concentrations of the drug were stated to have little or no adverse hemodynamic effects were mildly parasympatholytic and apparently had no effect on cardiac sympathetic nervous function In this initial study the effective antiarrhythmic concentration of disopyramide was one half to one third that of quinidine Subsequent interest in disopyramide in large part derived from the need to identify predictably effective antiarrhythmic drugs which are less toxic on acute and chronic administration than presently available agents

Clinical use and clinical toxicity

The efficacy of disopyramide in the treatment of cardiac arrhythmias has been well demonstrated First used in Europe disopyramide was employed successfully in the treatment of paroxysmal supraventricular tachycardias ventricular premature depolarizations (VPD s) and ventricular tachycardia [2-4] Other studies have confirmed the efficacy of disopyramide in reducing multi form VPD s and ventricular tachycardia [5,6] In addition, disopyramide has been useful in the prevention of recurrent atrial fibrillation follow ing cardioversion

The most complete compilation of the clinica antiarrhythmic effects of disopyramide wa reported in 1975 as part of a seminar organized b Searle Laboratories *

Vismara and colleagues reported that orall administered disopyramide significantly reduce the frequency of a variety of arrhythmias Of 1 patients 11 had multifocal VPD s, six had bifoca VPD s, one had unifocal VPD s, five had ventric ular tachycardia (VT) and one had atrial prema ture depolarizations (APD s) Significant reduc tions in the frequency of VPD s and in th severity of VT were induced by disopyramide a compared to placebo Following cessation of dis pyramide therapy and a return to placebo arrhythmias returned toward control levels Th efficacy of disopyramide also was studied in 1 ambulatory patients[8] of whom 77 had unifocal o multifocal VPD s 18 had VPD s and APD s an 18 had paroxysmal atrial tachycardia as well a APD s and VPD s In this group of 120 patient the average number of ectopic beats per hour wa approximately 260 Interestingly, administratio of placebo alone resulted in a significant reduc tion in the number of ectopic beats Howeve disopyramide 400 to 800 mg /day administere orally resulted in a statistically significan decrease (compared to placebo) in the averag number of ectopic beats Return to placeb resulted in a significant increase (compared t disopyramide) in the average number of ectopi beats

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* A seminar on Norpace (Disopyramide phosphate) A new antiarrhythmic agent Angiology 26 19 5

In a study of electrically induced atrial fibrilla on in three patients Befeler and associates[5] ported that disopyramide 2 mg/kg adminis red intravenously apparently elevated the rial fibrillation threshold

Disopyramide is well tolerated and the toxic fects that occur are primarily due to its anti olinergic actions Such side effects are reported be mild readily tolerated and transient[6] In an 3 week study of the comparative efficacy of sopyramide and quinidine in 124 patients the ifference between the percentage of individuals ho failed to complete the study because of side ffects (9 6 per cent for the disopyramide group vs 5 per cent for the quinidine group) was statis ically significant Nausea and vomiting urinary etention and somatic pain were the side effects eported from disopyramide Quinidine reactions ere more severe and consisted of severe dizzi ess, chills and fever and a generalized pruritic ash. Anticholinergic effects were less apparent in he disopyramide than in the quinidine group

Effects on atrioventricular conduction

Studies on conscious and pentobarbital anes thetized experimental animals given oral or parenteral doses of disopyramide have revealed prolongation of the P wave and QRS com plex and the P R interval The effects of disopyramide on QRS duration were less pro nounced than those of quinidine while those on P wave duration were equal to or greater than those of quinidine Correlative studies of the relation ship between plasma disopyramide levels and electrocardiographic changes have shown that these effects are concentration dependent

In studies using the His bundle recording tech nique parenterally administered disopyramide had no significant effect on sinus rate and A V nodal and intraventricular conduction It induced a slight decrease in the atrial effective refractory period and either had no effect on or prolonged the A V nodal functional refractory period and the relative refractory period of the His Purkinje system[5]

Comparison of the effects of disopyramide and quinidine on A V conduction in man suggest that disopyramide has less effect than quinidine on the A V node No increase in severity of A V block was observed in three patients who had A V block before disopyramide was administered and A V block did not occur as a result of disopyramide administration to 12 patients with normal A V conduction

Pharmacokinetics of disopyramide

The therapeutic plasma concentration range for disopyramide is 2 to 4 μg/ml (Dr D J McDermott Searle Labs personal communica tion) Following intravenous administration diso pyramide has a two stage elimination curve in experimental animals and man In man the first rapid phase of elimination of disopyramide from the blood (distribution phase) has a half time which varies from 3 to 5 minutes and is followed by a second slower (elimination) phase with a half time of 5 to [illegible] hours

Oral doses of disopyramide are reportedly completely absorbed Peak plasma levels are obtained ½ to 3 hours after administration and subsequently are maintained for 3 to 4 hours It has been stated that oral bioavailability of diso pyramide is 57 per cent that of the intravenously administered drug Whether metabolism differs significantly after oral and parenteral administra tion (as occurs for propranolol) has not been stated in the literature

Elimination of disopyramide is primarily renal with 40 to 60 per cent of an administered dose being excreted unchanged in the urine The major metabolite (15 to 25 per cent of single doses) is an [illegible] dealkylated form the antiarrhythmic activity of which is less than half that of the parent compound This too is excreted in the urine

Binding of disopyramide to human serum albumin is reported as 21 to 33 per cent It has been found that disopyramide and quinidine bind to separate sites on plasma proteins. This suggests that neither drug is likely to displace the other from protein binding sites Hence simulta neous administration of both drugs would be unlikely to raise the plasma concentration of the free form of either drug

Hemodynamic and autonomic effects of disopyramide in experimental animals and man

Disopyramide decreases cardiac output coro nary blood flow and myocardial contractility in intact dogs and decreases contractility in isolated perfused rabbit hearts The decrease in contractility induced by disopyramide was not

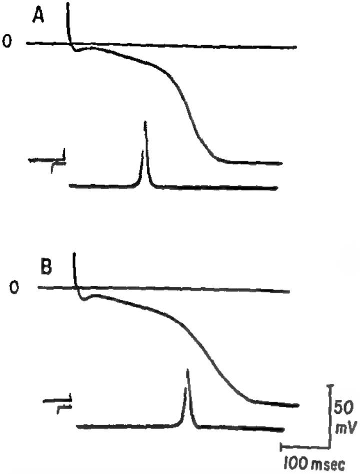

Fig 1 Effect of disopyramide 10 M on Purkinje fiber action potential Cycle length = 500 msec T=37 C In both panels the top trace is a reference zero potential the middle trace is an action potential recorded using an intracellular glass microelectrode the bottom trace is the electronically differentiated upstroke of a sawtooth wave with a rate of rise of 200 V/sec followed by the differentiated phase 0 upstroke of the action potential V_m *Panel A* is a control *Panel B* shows effects of disopyramide 10 M Note the decrease in action potential amplitude and V and the prolongation of the voltage-time course of repolarization These effects of disopyramide were readily reversible

prevented by previous administration of ouabain or digitoxin[1] Blood pressure was decreased by disopyramide, systolic pressure apparently more so than diastolic[1,11,16] This effect is most likely due to a decrease in cardiac output since disopyramide has no significant adrenergic blocking ability[10] Disopyramide exerts significant anticholinergic effects[1,17] For example, in animals disopyramide abolished the negative chronotropic effect of vagal stimulation and of exogenous acetylcholine and reduced acetylcholine induced hypotension[8]

Studies of the hemodynamic effects of disopyramide in man have revealed the following Cardiac output was decreased (≈ 18 per cent) following intravenous administration of disopyramide, 2 mg/kg, and a reflex increase (≈ 98 per cent) in systemic vascular resistance occurred in patients with clinical evidence of heart failure In addition, left ventricular dP/dt was decreased transiently (6 to 12 per cent) by disopyramide

Mechanism of antiarrhythmic action of disopyramide

Studies of the electrophysiologic properties of tissues from normal and diseased hearts have indicated that significant changes in action potential characteristics occur as a result of cardiac disease Normal atrial and ventricular muscle and specialized conducting fibers have rather high, electronegative resting membrane potentials and a rapid depolarization phase of the action potential This action potential has been referred to as the 'fast response' and it is responsible for propagation of activation through normal cardiac tissues[19] With the occurrence of disease (experimental or naturally occurring infarction or cardiac chamber dilatation) there is a decrease in resting membrane potential and action potential amplitude and upstroke velocity When membrane potential falls below approximately −55 mV a 'slow response' action potential occurs which has been implicated as a possible cause for reentrant arrhythmias Whereas the 'fast response' action potential is due primarily to a rapid inward ionic current carried by Na the slow response is the result of a much slower inward current carried primarily by Ca Specialized conducting fibers having slow or fast responses may develop automaticity That is they may depolarize spontaneously during electrical diastole giving rise to premature depolarizations or bursts of tachyarrhythmia

To alter the course of an arrhythmia associated with the electrophysiologic mechanisms described an antiarrhythmic drug would be expected either to (1) alter conduction in fibers having fast or slow response action potentials (2) prolong their refractory periods thereby limiting propagation of premature depolarizations or (3) depress automaticity

Procaine amide and quinidine have been found to decrease action potential amplitude and upstroke velocity and slow conduction in fast response fibers as well as prolong the effective refractory period and decrease automaticity

these actions are concentration dependent Diso-pyramide has effects on the fast response action potentials in rabbit atrial and canine Purkinje fibers[3, 4] that are similar to those of quinidine[4] and procaine amide[2] (Fig 1) It appears to have no effect on the slow response[4] By depressing conduction and prolonging refractoriness in cardiac fibers disopyramide may induce bidirectional block at sites where unidirectional block and re entry previously were occurring The disopyramide induced changes in conduction and refractoriness also are consistent with the in situ electrophysiologic studies in which P R and QRS prolongation were described[1]

The depressant effect of disopyramide on action potential characteristics is accentuated as extracellular potassium concentrations are increased This suggests that at high plasma potassium levels the therapeutic (and toxic) effects of disopyramide might be seen at lower plasma drug concentrations than would be expected were the potassium concentrations normal Similarly at low plasma potassium concentrations higher levels of disopyramide than normal may be required before an antiarrhythmic effect is seen

As has been described for other antiarrhythmic drugs disopyramide reduced automaticity Sekiya and Vaughan Williams showed that disopyramide decreased the frequency of spontaneous beating in isolated rabbit right atrial preparations although the effect apparently was less prominent with disopyramide than with quinidine Disopyramide caused a concentration dependent decrease in the slope of phase 4 depolarization of canine Purkinje fibers with a resultant decrease in automaticity

Conclusions

The cardiac effects of disopyramide closely resemble those of quinidine Both antiarrhythmic agents reduce action potential amplitude and upstroke velocity slow conduction and increase the effective refractory period of the A V node and His-Purkinje system Both exert a depressant effect on myocardial contractility and have anticholinergic properties However disopyramide unlike quinidine does not alter sympathetic function. Disopyramide reportedly causes fewer anticholinergic side effects than quinidine and has been described as comparable to quinidine in the therapy of a broad spectrum of atrial and ventricular arrhythmias As such it appears that disopyramide may offer a useful alternative to quinidine or procaine amide for treating patients whose arrhythmias are unresponsive to therapy with those drugs or who have developed toxic manifestations of quinidine or procaine amide therapy

REFERENCES

1 Mokler C M and Van Arman C G Pharmacology of a new antiarrhythmic agent γ-diisopropylamino α phenyl α (2 pyridyl) butyramide (SC 7031) J Pharmacol Exp Ther 136 114 1962
2 Colonna D Disopyramide et troubles du rythme cardiaque Gaz Medic France 76 6609 1969
3 Desruelles J Gerard A Ducatillon P and Herbaux A Nos premiers essais cliniques de disopyramide dans le troubles du rythme cardiaque, Therapie 22 93 196
4 Granier J Un nouvel antiarhythmique Disopyramide Press Med 76 1603 1968
5 Befeler B Costellanos A Wells D E Vagnerio M D and Yeh B K Electrophysiologic effects of the antiarrhythmic agent disopyramide phosphate Am J Cardiol 35 282 1975
6 Vismara L A Mason D T and Amsterdam E A Disopyramide phosphate Clinical efficacy of a new oral antiarrhythmic drug Clin Pharmacol Exp Ther 16 330 1974
7 Hartel G Louhija A and Konttinen A Disopyramide in the prevention of recurrence of atrial fibrillation after electroconversion Clin Pharmacol Ther 15 551 1974
8 Smith W S Clinical studies of Norpace Part I Angiology 26 124 1975
9 Oshrain C Arif M Laidlaw J C Cook W H and Willis, P A double blind comparison of disopyramide phosphate and quinidine sulfate as antiarrhythmic agents, G D Searle & Co Communication 1975
10 Mathur P Cardiovascular effects of a newer antiarrhythmic agent disopyramide phosphate AM HEART J 84 64 1972
11 Ranney R E Dean R R Karim A and Radzialowski F M Disopyramide phosphate Pharmacokinetic and pharmacologic relationships of a new antiarrhythmic agent, Arch. Int Pharmacodyn 191 162, 1971
12 Josephson M D Caracta A R Lau S H Gallagher J J and Damato A N Electrophysiological evaluation of disopyramide in man AM HEART J 86 771 1973
13 Karim A The pharmacokinetics of Norpace Angiology 26 85 1975
14 Wit A L Hoffman B F and Rosen M R Electrophysiology and pharmacology of cardiac arrhythmias IX Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade Part B AM HEART J 90 665 1975
15 Chien Y W Lambert H J and Karim A Comparative binding of disopyramide phosphate and quinidine sulfate to human plasma proteins, J Pharm Sci 63 1877 1974
16 Yeh, B K Sung, P K and Scherlag B J Effects of disopyramide on electrophysiological and mechanical properties of the heart J Pharm Sci 62 1024 1973
17 Mokler C M and Hillman R A Nature of the

anticholinergic action of some antiarrhythmic drugs Pharmacol Res Comm 4 171 1972

18 Willis P W The hemodynamic effects of Norpace II Angiology 26 106 1975

19 Wit A L Rosen M R and Hoffman B F Electrophysiology and pharmacology of cardiac arrhythmias II Relationship of normal and abnormal electrical activity of cardiac fibers to the genesis of arrhythmias AM HEART J 88 515 1974

20 Cranefield P F Wit A I and Hoffman B F Conduction of the cardiac impulse III Characteristics of very slow conduction J Gen Physiol 59 227 1972

21 Hoffman B F The action of quinidine and procaine amide on single fibers of dog ventricle and specialized conductive system Anais Acad Brasil Cienc 29 336 1958

22 Rosen M R Merker C Gelband H and Hoffman B F Effects of procaine amide on the electrophysiologic properties of the canine ventricular conduction system J Pharmacol Exp Ther 185 438 1973

23 Danilo P Hordof A and Rosen M R Effects of disopyramide phosphate (Norpace) on electrophysiologic properties of isolated canine cardiac Purkinje fibers Am J Cardiol 35 130 1975

24 Kus T and Sasyniuk B I Electrophysiological actions of disopyramide phosphate on canine ventricular muscle and Purkinje fiber Circ Res 37 884 1975

25 Rosen M R and Hoffman B F Mechanisms of action of antiarrhythmic drugs Circ Res 32 1 1973

26 Sekiya A and Vaughan Williams E M A comparison of the antifibrillatory actions and effects on intracellular cardiac potentials of pronethalol disopyramide and quinidine Br J Pharmacol 26 473 1963

The influence of inspiration on angina pectoris – clue to right coronary artery disease

ght ventricular ischemia has been suggested as a possible echanism of chest pain in various disorders of right ventric ar pressure overload including pulmonic stenosis idio thic pulmonary hypertension chronic pulmonary fibrosis d emphysema, and mitral stenosis Recently the clinical d hemodynamic features of right ventricular infarction ve been outlined but right ventricular angina secondary to ronary artery disease has never been clearly identified and parated from left ventricular angina

We have recently seen a 45-year-old physician who presented with exercise related but atypical angina pectoris The est pain was clearly accentuated by inspiration On each casion the patient s pain was provoked by the usual kind of ertion which causes angina such as climbing a hill carrying heavy weight etc Once the pain was established inspiration ould consistently make the pain worse and relief would ccur on each expiration During subsequent evaluation and vestigation the patient developed an acute inferior wall myocardial infarction Although this patient never underwent ardiac catheterization and coronary arteriography the question of the mechanism of inspirational angina as proposed here was suggested by this myocardial infarction

The anterior and lateral aspects of the right ventricle and frequently the entire right ventricle is perfused primarily by the right coronary artery During inspiration the increase in venous return results in increased right ventricular myocardial fiber stretch and hence an increase in contractility Oxygen consumption will therefore rise until venous return diminishes. In addition there may be an inspirational increase in heart rate Both of these factors may lead to an increase in right ventricular myocardial oxygen consumption during the period of heightened venous return Significant obstructive disease of the right coronary artery then could cause an imbalance of right ventricular myocardial oxygen supply and demand and hence the production of angina emanating from the right ventricle

From the location of his myocardial infarction one would expect that our patient had disease of his right coronary arterial tree. The description of exertional chest pain which was clearly intensified with each inspiration is most unusual in angina pectoris and we therefore propose that this sign may suggest disease of the right coronary artery

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REFERENCES

1 Lasser R P and Genkins G Chest pain in patients with isolated pulmonic stenosis Circulation 15 258 1957
2 Dresdale D T Michtom R J and Schultz, M Recent studies in primary pulmonary hypertension during pharmacodynamic observations on pulmonary vascular resistance Bull N Y Acad Med 30 19 1954
3 Viar W N and Harrison R Chest pain in association with pulmonary hypertension Its similarity to the pain of coronary disease Circulation 5 1 1952
4 Burgess, A and Ellis, L. B Chest pain in patients with mitral stenosis with particular reference to so called hypercyanotic angina N Engl. J Med. 226 937 1942
5 Cohn J N Guiha, N H Broder M I and Limas C J. Right ventricular infarction Am J Cardiol 33 209 1974

Improvement in prognosis of myocardial infarction by long term beta adrenoceptor blockade

A recent report concerns a double blind multicenter trial of a beta adrenoceptor blocking agent practolol in the long term treatment of 3 038 patients recovering from myocardial infarction. Patients were randomly allocated to drug or placebo one to four weeks following the acute attack and were treated for periods of about a year Some continued for two to three years Mortality rates and morbidity were studied

There was a statistically significant reduction in over all deaths in the practolol treated group ($P < 0.02$) which was virtually confined to the sub-group whose infarcts prior t

entry were situated anteriorly (22 drug v 48 placebo $P < 0.005$). Sudden deaths, arbitrarily defined as deaths within 2 hours of symptoms of a new event, were significantly reduced (30 v 52, $P < 0.02$), the effect being seen in patients with pre-entry inferior as well as those with pre-entry anterior infarction. However, in patients with pre-entry inferior infarction there was an increased mortality rate in the 2 to 24 hours following a new event, thus no over-all reduction in mortality was evident.

In planning the trial originally, the possibility that sudden death might be reduced by long-term therapy with beta blockers was amply supported by animal experimentation showing the importance of sympathetic nervous activity in the production of death following experimental myocardial infarction and its prevention by propranolol and other beta adrenoceptor blocking agents. The probability that patients with pre-entry anterior infarction might benefit specially from long-term beta blocking therapy did not occur to us, though with hindsight perhaps it should have done; the high sudden death rate in the early months following anterior infarction had been fairly widely accepted clinically, if not well documented. In our trial no less than 19 of the 20 deaths in the placebo group occurring in the first month after entry to the trial were found to have sustained pre-entry anterior infarction (lateral and anteroseptal counted as anterior). Pre-entry anterior infarction was correlated with an increased incidence of tachyarrhythmias causing withdrawal from the trial or recorded at follow-up visits to the clinics. In the treatment group these arrhythmias were reduced to a significant extent only in the patients who had suffered pre-entry anterior infarction. (A more detailed analysis of this is being carried out.) Perhaps also relevant to the results was the highly significant finding that two-thirds of the patients with anterior reinfarction recorded during the trial had suffered anterior infarction prior to entry ($P < 0.01$). Linden reported a similar tendency to reinfarct at the same site. His numbers were small but convincing for anterior infarction. Reinfarction anteriorly would lead to an increased incidence of tachyarrhythmias in patients immediately following reinfarction, as was well documented by Webb and colleagues. Such potentially fatal arrhythmias should be partially suppressed by prophylactic beta blockade, as they are in experimental animals.

Another interesting finding in the trial was the significant association between blood pressure below the mean at entry and protection by beta blocker therapy. Again there was some evidence of an association with cardiac arrhythmias. In the placebo group the numbers of patients withdrawn from the trial because of arrhythmias were significantly higher for patients with below average blood pressure at entry. A more detailed analysis of blood pressure in relation to other variables is currently in progress.

The findings of the trial suggest that long-term treatment with practolol for patients recovered from anterior myocardial infarction might reduce the death rate to about half over periods of 1 to 3 years. Because of the serious side effects now known to be caused by practolol, the drug is contraindicated for treatment longer than a month. However, it seems very probable that the life-saving effects in the trial were due to its antiarrhythmic effect as a beta adrenoceptor blocking agent and that other similar agents would produce similar results. Alprenolol has already been shown to be effective, though the trials involved very small numbers. Evidence of reduced C.H.D. mortality in patients receiving propranolol for angina pectoris and hypertension indirectly support the supposition that beta blockade is the operative factor.

The participants in the practolol trial recommended that long-term beta adrenoceptor blocking therapy should be given to patients recovered from the acute phase of anterior myocardial infarction, unless specific contraindications exist.

In view of the reduction in the number of sudden deaths (< 2 hours), similar recommendations may be made for patients with inferior infarction, but the smaller number of deaths following inferior infarction and the increase in mortality in the 2 to 24 hour period indicate that further investigation is required on this aspect. The fact that 7 of the 8 deaths in the first month following inferior infarction were in the drug-treated group suggests that the initiation of therapy might be postponed for a few weeks, but again the small numbers do not permit one to be definite. If and when a fresh event should occur, and if the patient should survive long enough to receive medical attention, the possibility of using atropine might be considered for selected cases to cover the 4 hours necessary for the effects of beta blockade to wear off.

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REFERENCES

1. Green, K. G. (trial coordinator) and 76 other authors: Improvement in prognosis of myocardial infarction by long-term beta adrenoreceptor blockade using practolol, Br. Med. J. 3:735, 1975.
2. Schwartz, P. J.: Role of catecholamines in arrhythmias after acute myocardial infarction, Lancet 1:1340, 1975.
3. Pentecost, B. L., and Austen, W. G.: Beta adrenergic blockade in experimental myocardial infarction, Am. Heart J. 72:791, 1966.
4. Khan, M. I., Hamilton, J. T., and Manning, G. W.: Protective effect of beta adrenoceptor blockade in experimental coronary occlusion in conscious dogs, Am. J. Cardiol. 30:832, 1972.
5. Linden, V.: Anterior and inferior myocardial infarction: Comparison with regard to some diseases and background factors, Br. Heart J. 36:1032, 1974.
6. Webb, S. W., Adgey, A. A. J., and Pantridge, J. F.: Autonomic disturbance at onset of myocardial infarction, Br. Med. J. 3:89, 1972.
7. Lown, B., and Wolf, M.: Approaches to sudden death from coronary heart disease, Circulation 44:130, 1971.
8. Wilhelmsson, C., Vedin, J. A., Wilhelmsen, L., Tibblin, G., and Werko, L.: Reduction of sudden deaths after myocardial infarction by treatment with alprenolol, Lancet 2:1157, 1974.
9. Ahlmark, G., Saetre, H., and Korsgren, M.: Reduction of

sudden deaths after myocardial infarction Lancet 2 1563, 19 4
Amsterdam, E A Wolfson S and Gorlin R Effect of therapy in angina pectoris Ann Intern Med 68 1151 1968.
Lambert D M B Beta blockers and life expectancy in ischaemic heart disease Lancet 1 93 1972
12 Lambert D M D Hypertension and myocardial infarction Br Med J 3 685 1974
13 Stewart I McD G A prospective study of the comparative incidence of myocardial infarction in essential uncomplicated hypertensives under treatment containing or excluding a beta adrenergic blocking agent Clin Sci Mol Med Suppl 3 (In press 1976)

The etiology of sino atrial disorder (Sick Sinus Syndrome)

Chronic sino-atrial disorder (Sick Sinus Syndrome) is being found in patients with increasing frequency but its etiology remains a mystery The acute form of the syndrome was initially described after electrical reversion of cardiac arrhythmias, but the commonest association in clinical practice is with myocardial infarction Here sinus bradycardia or sinus arrest with junctional takeover sometimes associated with other disturbances of atrial rhythm is often seen soon after inferior myocardial infarction Although normal sinus rhythm almost invariably returns if the patient survives it is not unreasonable to suppose that the chronic form of sino atrial disease might also be due to interference with the blood supply to the sinus node and atrium The report of features of coronary artery disease in 15 (48 per cent) of 31 patients with the bradycardia tachycardia syndrome supports this theory However we obtained contrary results in the survey of a larger group of patients initiated in Devon in 1968 the incidence of myocardial infarction in patients with complete block (a condition which was also once thought to be due to coronary artery disease) was 29 (13 per cent) out of 222 patients whereas in sino atrial disorder the incidence was 11 (10 per cent) of 106 cases.

There are very few reports of postmortem studies of the specialized cardiac tissues or their blood supply in patients dying with chronic sino-atrial disorder because of the difficulty in obtaining material with adequate clinical information and the laborious nature of the pathological technique Several descriptions of individual cases emphasize the finding of atheroma with arteriosclerosis of the major coronary or sinus node arteries with or without associated sclerosis of the sino-atrial node and right atrium In a recent study of eight cases, the major coronary vessels were free from atheroma in seven and in the one case with atheroma the sino atrial artery was spared and filled well with contrast media on postmortem angiography In this series the histology of the sino-atrial node was grossly abnormal in seven instances. The node and atrium were heavily infiltrated with amyloid material in one case. In the other six cases the specialised muscle cells in the sino-atrial node were very scanty or had virtually disappeared and the node was either small or largely replaced with fibrous tissue Warembourg and associates described complete destruction of all the connections which normally exist between atrial muscle and the sino-atrial node in their case and pathological changes in the atrial muscle of the sino atrial approaches were found in all the eight cases described above

It has been suggested that some instances of sino atrial disorder may be congenital and it is tempting to regard the instances of small and apparently atrophic sino atrial nodes as being the result of a congenital abnormality Nevertheless the patients coming to autopsy were elderly and a degenerative process would be equally possible Again the fibrosis in the node and atrium may represent a non specific end result of one of a number of past pathological processes such as pericarditis, rheumatic fever or diphtheria Scandinavian authors have incriminated diphtheria but this is unlikely to be a common factor universally and in the Devon survey a history of diphtheria was found in only 9 per cent of patients with sino atrial disorder an incidence identical to that found in patients with complete heart block. An auto immune mechanism has been invoked as responsible for some cases of heart block and this may apply in sino atrial disease Certainly there are similarities between the two conditions and conduction disturbances are common in sino atrial disease but the usual site of the block and the age distribution differ

It is dangerous to draw dogmatic conclusions concerning the effect that pathological changes may have upon the electrophysiology of the heart particularly since the precise number and grouping of automatic cells required to form a pacemaking center in man are still unknown Nevertheless the gross reduction in number and density of the specialized muscle cells in the sino atrial nodes of most patients with sino-atrial disease may predispose to failure of impulse formation or the generation of a sub threshold impulse Furthermore the severe pathological changes in the sino-atrial node approaches imply that, contrary to previous theory a physical basis for sino-atrial block may exist

Undoubtedly in some instances of established sino atrial disease the blood supply to the sino atrial node remains intact and the degree of fibrosis is no more than can be expected from the normal ageing process. Here some extra-cardiac factor such as excessive vagal tone or a cerebral lesion might be incriminated However such a mechanism seems unlikely since far from atropine abolishing the dysrhythmia in sino-atrial disorder the response is usually subnormal. In one case carcinomatous infiltration of the cardiac plexus was found at autopsy and it is possible that this might have increased the parasympathetic drive to the sinus node although the author considered this unlikely More likely alternatives would seem to be degeneration of the perinodal

ganglionated plexus or reduction of cholinesterase activity in atrial tissue either of which would be indiscernible on routine light microscopy

Sino atrial disorder is likely to be the end result of one of a number of pathological processes which interfere with sino atrial node and atrial muscle function From the very limited data available it seems unlikely that coronary artery disease plays a major role in producing the chronic form of the disorder Rather conditions leading to atrophy or fibrosis should be sought

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REFERENCES

1 Lown B Electrical reversion of cardiac arrhythmias Br Heart J 29 469 1967
2 James T N The coronary circulation and conduction system in acute myocardial infarction Progr Cardio vasc Dis 10 410 1968
3 Rokseth R and Hatle L Sinus arrest in acute myocardial infarction Br Heart J 33 639 1971
4 Ferrer I The sick sinus syndrome Circulation 47 635 1973
5 Sutton R Norman J and Briers L Sick sinus syndrome Br Med J 3 367 1975
6 Conde C A Leppo J Lipski J Stimmel B Litwak R Donoso E and Dack S Effectiveness of pacemaker treatment in the bradycardia tachycardia syndrome Am J Cardiol 32 209 1973
7 Shaw D B and Eraut D Prevalence and morbidity of heart block in Devon Br Med J 1 144 1970
8 Shaw D B Kekwick C A and Brownlee W C Sick sinus syndrome Br Med J 3 767 1975
9 Rosen K M Rahimtuola S H Cunnar R M and Lev M Transient and persistent atrial standstill with His bundle lesions Circulation 44 220 1971
10 Kaplan B M Langendorf R Lev M and Pick A Tachycardia bradycardia syndrome (so called Sick Sinus Syndrome) Am J Cardiol 31 497 1973
11 Kulbertus H E Leval Rutten F and Demoulin J C Sinu atrial disease A report of 13 cases J Electrocardiol 6(4) 303 1973
12 Warembourg H Thetry C I Lekieffre J Delbecque H and Gosselin B Blocs Sino Auriculaires et blocs auriculo ventriculaires associéts Arch Mal Coeur 67 787 1974
13 Brownlee W C Evans R C and Shaw D B Pathology of conducting system in sino atrial disease Br H J 37 779 1975
14 Williams D O Jones E L Nagle R E and S R S Familial atrial cardiomyopathy with heart b Q J Med 41 491 1972
15 Radford D J and Izukawa T Sick sinus syndr Arch Dis Child 50 879 1975
16 Rokseth R Hatle L Gedde Dahl D and Foss P Pacemaker therapy in sino atrial block compl a paroxysmal tachycardia Br Heart J 32 93 1970
17 Rasmussen K Chronic sino atrial heart block HEART J 81 38 1971
18 Fairfax A J and Leatham A Idiopathic heart b Associated with vitiligo thyroid disease pernic anaemia and diabetes mellitus Br Med J 4 322 19
19 Fowler P B S Ikram H Maint R N Makey A and Kirkham J S Bradycardia with angina Haemo namic aspects with treatment Br Med J 1 92 1969
20 Eraut D and Shaw D B Sinus bradycardia Br He J 33 742 1971
21 Narula O S Atrio ventricular conduction defects patients with sinus bradycardia Circulation 44 10 1971
22 Evans R C Kekwick C A and Shaw D B Overdri suppression and other tests of sino atrial function B Heart J 37 559 1975
23 Scherf D The mechanism of sino atrial block Am Cardiol 23 769 1969
24 Lev M J Ageing changes in the human sinu atria node J Gerontol 9 1 1954
25 Davies M and Pomerance A Quantitative study o ageing changes in the human sino atrial node and in er nodal tracts Br Heart J 34 150 1972
26 Laslett E E Syncopal attacks associated w prolonged arrest of the whole heart Q J Med 2 1909
27 Webb A M and Wilson D C Standstill of the heart of vagal origin AM HEART J 5 493 1930
28 Kirk J E and Kvorning S A Sinus bradycardia clinical study of 515 consecutive cases Acta Med Scand (Suppl) 266 625 1952
29 Easley R M and Goldstein S Sino atrial syncope Am J Med 50 166 1971
30 Mandel W J Hayakawa H Allen H N Danzig R and Kermaier A I Assessment of sinus node function in patients with the sick sinus syndrome Circulation 46 761 1972
31 Pearson R S B Sinus bradycardia with cardiac asystole Br Heart J 12 61 1950
32 Rossi L Histopathologic features of cardiac arrhythmias Casa Editrice Ambrosiana Milano 1969
33 Dighton D H Sinus bradycardia Autonomic influences and clinical assessment Br Heart J 36 91 1974

Of the cardiac work-up

There is a practice in most hospital and medical institutions and office groups to do a complete work up of patients This modern work up is looked upon with pride and with a sense of superiority It is considered superior to the work up of equally competent if not more competent physicians who fortunately do not have access to expensive gadgetry and hazardous procedures Today these centers routinely include along with EPA and lateral roentgenographic views of the heart,

G CBC urine analysis and SMA other studies such as ...dmill exercise testing coronary angiography ECHO lung ...n (and other scans at times) innumerable consultation ...ts, and many repeated unnecessary tests and examina...s. These special studies are frequently followed by ...onary artery bypass surgery a procedure yet to be care...ly and fully evaluated That these special procedures are ...zardous is evident from the requirements of standby defi...llators, potent drugs, endotracheal tubes ready anesthesi...ogists, surgeons, trained nurses and physicians. The "crash ...t" is always nearby Why? More importantly many if not ...st of these procedures are poorly recorded too often too ...oneously recorded to be reliable and thus are misleading ...Where is the bedside cardiology? In fact where is the clinical cardiology? What is the service rendered? What about the cost to the patient? (The people pay for this regardless of the source of the money) And when by whom and by what means will this unnecessary expensive poorly recorded and usually useless hazardous practice be evaluated and modified? It is time to take serious constructive note of the modern practice" of cardiology The better the clinical cardiologist the less he needs from the laboratory to complete his investigations and the cardiac work up

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Letters to the Editor

Reducing substances in certain heparin preparations a source of error in the measurement of indocyanine green

To the Editor

Indocyanine green dilution is one of the most common methods to measure cardiac output As with other indicator dilution methods accuracy is dependent upon the stability of the indicator injected The dye has been reported to be exquisitely sensitive to minute concentrations of reducing agents in one brand of heparin (Lipo Hepin Riker Laboratories) resulting in an average reduction in optical density of 72 per cent Information is not available in the literature concerning the presence of reducing substances in other existing brands * Since heparin is an organic acid the effect of serum heparin concentration and biological variation in strength should be considered The common use of systemic heparinization during cardiac catheterization warrants knowledge of its reducing strength when indocyanine green dilution is employed to measure cardiac output

We have investigated six brands of heparin that are widely used Heparin was added to the pooled human plasma to produce concentrations of 4 20 and 40 units per ml to simulate heparin concentrations reached in vivo during catheterization procedures or in the pooled samples when heparin is used in arterial withdrawal systems

Indocyanine green was diluted to 5 mg /c c with diluent supplied by the company A calibrated microliter syringe was used to add the dye to plasma in five different concentrations (19 39 58 77 and 97 mg /L) A transmission cuvette densitometer known to have linear deflection to dye concentrations (0 to 40 mg /L) in plasma was employed A standard physiological recorder was used to record calibration points

The calibration of dye in plasma was found to be linear and reproducible for the dye concentrations when tested by linear regression analysis (γ = 0 995 SEE = 0 21 mg /L) † The reproducibility of a single calibration point was excellent (S D = 0 06 mg /L) ‡ The slope of the dye calibration curve did not vary at heparin concentrations of 4 20 and 40 units/ml with three brands of heparin

The heparin preparation previously reported to cause a 72 per cent reduction of the dye calibration slope was found to cause a 20 per cent reduction in our study at the same dye and heparin concentration (Lipo Hepin) A second brand of heparin was found to cause a 54 per cent error in the calibration slope (Sodium heparin injection intestinal mucosa Upjohn) This finding was reproducible on two successive days when different vials of the same batch were tested but was not seen when additional heparin batches were tested A third brand was found to cause a reduction in the d e calibration slope of 30 per cent (Panheparin Abbott) The other three brands were not found to affect the slope of the dye calibration curve with the batches tested When d reduction caused a change in the calibration slope l a n was maintained

We have found that the concentration of red substances varies in different batches and brands of hepa Three brands were found to contain reducing substances some of the batches tested Communicati with th processing companies has revealed that varying amounts sodium bisulfite is used by four companies in the processing different batche of heparin (Abbott Riker Upjohn [intestinal mucosa] and Rics) Two companies do not use t reducing substance (Upjohn [beef lung] and Organon)

Thus care must be exercised in the choice of heparin u during cardiac catheterization Preparations without redu substances would seem to be the best choice if indocyan green is to be used to measure cardiac output Since reduction by sodium bisulfite is found to cause a change in calibration slope without affecting linearity the linearity dye calibration points by regression analysis is not a test of absence of dye reduction Although heparin is a weak orga acid systemic heparinization concentration levels are found to reduce indocyanine green concentration w heparin preparations without reducing agents are used

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REFERENCES

1 Cobb L A and Barnes S C Effects of reducing a on indocyanine green dye Am HEART J 70 145 1
2 Sutterer W R Hardin S E Benson R W hn L J and Schiebler G L Optical behavior of cyanine green dye in blood and in aqueous solution HEART J 72 345 1966

* Liquaemin Sodium 100" Organon Inc Bio hepin Rics Biological Inc Panheparin Abbott Laboratories Lipo Hepin Riker Laboratories Sodium heparin injection intestinal mucosa and beef lung Upjohn Company

† γ = correlation coefficient SEE = Standard error of estimate

‡ S D = Standard deviation

Subendocardial infarction What happens la

To the Editor

This letter describes the follow up of patients who discharged from the hospital with a diagno is of subenc dial infarction

A typical patient s course is as follows The che t pain few hours duration There is no history of heart disease electrocardiogram shows symmetrically inverted T wa several leads and the patient is admitted to the Coronary Unit The T waves remain inverted for at least three da

sequently return to normal configuration Occasionally re will be moderate elevations of the cardiac enzymes but ually they are normal The patient is not anemic has no ctrolyte abnormality has not had a pulmonary embolus or y other disorder respon ible for the abnormal repolarization n in the ECG

Symmetrically inverted T waves have been u ed as one of e criteria for the diagnosis of a subendocardial myocardial farction. The number of autopsies reported has been all. These patients have damaged only a limited area of the yocardial muscle mass Their hospital course is benign

We reviewed the records of 500 patients (1968 and 1970) who d the discharge diagnosis of "Myocardial Infarction" The st majority of these patients were eliminated from this nalysis because they had transmural myocardial infarction a history of previous cardiac disease or they had no follow p after their discharge There were 22 patients—twelve male nd ten female—who had experienced chest pain of at least ne hour duration had symmetrically inverted T waves existing three or more days, had no prior cardiac history and ad been followed after hospital discharge Seventeen patients ad no significant enzyme elevations. The remaining five had levation of CPK SGOT and LDH The average follow up for he whole group was 34 months Six patients developed a ransmural infarction during the follow up period, ranging rom 1 to 60 months. Sixteen patients, followed from 8 to 63 months, did not develop a myocardial infarction Two of the five patients with enzyme elevations (CPK SGOT LDH) and our of 17 without enzyme elevations developed a transmural myocardial infarction (27 3 per cent)

One other patient developed complete heart block requiring the insertion of a permanent pacemaker he has been well for more than four years. Another patient had four separate episodes of chest pain and symmetrically inverted T wave within a nine month period until he was lost to follow up A third patient later had a normal coronary arteriogram

The inferences we draw are as follows (1) Although the incidence of subendocardial myocardial infarction is relatively small, a significant number of these patients will go on to develop a transmural myocardial infarction and (2) those patients who later do develop a transmural myocardial infarc tion will usually do so in the same anatomical area as their original injury

Since a significant number of these patients ha e coronary artery disease which is sufficient enough to cause occlusion and transmural infarction at a later date perhaps these are the patients who might benefit from coronary arteriography in a search for a surgically correctable lesion

Further study of patients such as those investigated here is needed.

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REFERENCES

1 Cook R W Edwards, J E and Pruitt R D Circulation 18 603 and 613 1958
2 Madias J E Chahine R A., Gorlin R and Blacklow D J A comparison of transmural and nontransmural acute myocardial infarction Circulation 49 498, 1974
3 Kaplin B M and Berkson D M Serial electrocardiograms after myocardial infarction Ann Intern Med 60 430 1964

Severe mitral valve disease in children

To the Editor

We read with interest the paper entitled "Surgical management of severe mitral valve disease in childhood" by Drs. Gotsman and Van der Horst which appeared in the AMERICAN HEART JOURNAL (90 685 1975) Although we agree with the authors on many points our large experience with children with rheumatic heart disease who are severely incapacitated and require surgery as early as eight years of age has led us to several different conclusions

1 Valve calcification in our series of 60 children has been extremely rare before age 15 This is in contrast with the 10 per cent figure quoted in the paper

2 The advanced and the awkward pathology of stenotic mitral valves in these children with deformity and fibrosis of the papillary muscles, shortening of chordae tendineae inward rolling and adhesion of the cusps, together with their elastic consistency makes them extremely poor candidates for closed commissurotomy The valves that we encounter often need a meticulous commissurotomy under direct vision Yet a number of these patients have done poorly even after open commissurotomy and have required valve replacement later Despite the inconveniences of two operations we prefer this approach since initially in many cases of mitral stenosis not amenable to commissurotomy an adequately large prosthesis cannot be inserted resulting in poor hemodynamic response

3 Because the left ventricle becomes smaller following successful prosthetic mitral and/or aortic valve replacement a low profile valve such as Bjork Shiley prosthesis is preferred for children

4 Our experience with prosthetic mitral valve replacement in children has been extremely rewarding with a zero mortality rate in 30 children

5 Although the authors obtained apparently good results without anticoagulation we strongly recommend routine and adequate anticoagulation therapy with frequent follow up examinations.

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REFERENCE

1 Aryanpur I Shakibi, J Siassi B and Pavdar M Regression of pulmonary hypertension following mitral valve surgery in children Presented at the 13th World Congress of Cardiology Edinburgh September 1975

Reply

To the Editor

I wish to thank Drs. Aryanpur and Shakibi for their letter

Letters to the Editor

Reducing substances in certain heparin preparations: a source of error in the measurement of indocyanine green

To the Editor

Indocyanine green dilution is one of the most common methods to measure cardiac output. As with other indicator dilution methods, accuracy is dependent upon the stability of the indicator injected. The dye has been reported to be exquisitely sensitive to minute concentrations of reducing agents in one brand of heparin (Lipo Hepin, Riker Laboratories), resulting in an average reduction in optical density of 72 per cent.[1] Information is not available in the literature concerning the presence of reducing substances in other existing brands.[2] Since heparin is an organic acid, the effect of serum heparin concentration and biological variation in strength should be considered. The common use of systemic heparinization during cardiac catheterization warrants knowledge of its reducing strength when indocyanine green dilution is employed to measure cardiac output.

We have investigated six brands of heparin that are widely used.* Heparin was added to the pooled human plasma to produce concentrations of 4, 20, and 40 units per ml. to simulate heparin concentrations reached in vivo during catheterization procedures or in the pooled samples when heparin is used in arterial withdrawal systems.

Indocyanine green was diluted to 5 mg./c.c. with diluent supplied by the company. A calibrated microliter syringe was used to add the dye to plasma in five different concentrations (1.9, 3.9, 5.8, 7.7, and 9.7 mg./L.). A transmission cuvette densitometer known to have linear deflection to dye concentrations (0 to 40 mg./L.) in plasma was employed. A standard physiological recorder was used to record calibration points.

The calibration of dye in plasma was found to be linear and reproducible for the dye concentrations when tested by linear regression analysis (γ = 0.995, SEE = 0.21 mg./L.).† The reproducibility of a single calibration point was excellent (S.D. = 0.06 mg./L.).‡ The slope of the dye calibration curve did not vary at heparin concentrations of 4, 20, and 40 units/ml. with three brands of heparin.

The heparin preparation previously reported to cause a 72 per cent reduction of the dye calibration slope was found to cause a 20 per cent reduction in our study at the same dye and heparin concentration (Lipo Hepin). A second brand of heparin was found to cause a 54 per cent error in the calibration slope (Sodium heparin injection, intestinal mucosa, Upjohn). This finding was reproducible on two successive days when different vials of the same batch were tested, but was not seen when additional heparin batches were tested. A third brand was found to cause a reduction in the dye calibration slope of 30 per cent (Panheparin, Abbott). The other three brands were not found to affect the slope of the dye calibration curve with the batches tested. When dye reduction caused a change in the calibration slope, linearity was maintained.

We have found that the concentration of reducing substances varies in different batches and brands of heparin. Three brands were found to contain reducing substances in some of the batches tested. Communication with the processing companies has revealed that varying amounts of sodium bisulfite is used by four companies in the processing of different batches of heparin (Abbott, Riker, Upjohn [intestinal mucosa], and Ries). Two companies do not use this reducing substance (Upjohn [beef lung] and Organon).

Thus, care must be exercised in the choice of heparin used during cardiac catheterization. Preparations without reducing substances would seem to be the best choice if indocyanine green is to be used to measure cardiac output. Since dye reduction by sodium bisulfite is found to cause a change in the calibration slope without affecting linearity, the linearity of dye calibration points by regression analysis is not a test of the absence of dye reduction. Although heparin is a weak organic acid, systemic heparinization concentration levels are not found to reduce indocyanine green concentration when heparin preparations without reducing agents are used.

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REFERENCES

1. Cobb, L. A., and Barnes, S. C.: Effects of reducing agents on indocyanine green dye, Am. Heart J. 70:145, 196[illegible].
2. Sutterer, W. R., Hardin, S. E., Benson, R. W., Krovetz, L. J., and Schiebler, G. L.: Optical behavior of indocyanine green dye in blood and in aqueous solution, Am. Heart J. 72:345, 1966.

Subendocardial infarction: What happens later

To the Editor

This letter describes the follow-up of patients who were discharged from the hospital with a diagnosis of subendocardial infarction.

A typical patient's course is as follows. The chest pain is of a few hours duration. There is no history of heart disease. The electrocardiogram shows symmetrically inverted T waves in several leads and the patient is admitted to the Coronary Care Unit. The T waves remain inverted for at least three days and

*Liquaemin Sodium "100," Organon Inc.; Bio-heprin, Ries Biological Inc.; Panheparin, Abbott Laboratories; Lipo Hepin, Riker Laboratories; Sodium heparin injection, intestinal mucosa and beef lung, Upjohn Company.

†γ = correlation coefficient; SEE = Standard error of estimate.

‡S.D. = Standard deviation.

Progress in Cardiology Edited by Paul N Yu MD and J F Goodwin MD Philadelphia 19 5 Lea & Febiger Publishers, 224 pages. Price $15.00

The fourth volume of *Progress in Cardiology* by Yu and Goodwin includes 9 chapters on interesting and timely subjects in cardiology These chapters are on echocardiography prolapse of the mitral valve digitalis toxicity quantitative left ven riculography high altitude pulmonary hyperten sion and edema coronary artery disease in children lysosomes the cardiovascular system cardiac enzymes in the serum and prevention of cell death. These chapters are interesting and authoritative for the most part Cardiologists and internists who do not follow the literature closely will find this volume to be of interest Unfortunately some of the contributors are not directly involved in a study of their subject Their presentations represent only a selected review of the literature Cardiologists who have limited time for reading will find volume 4 as the previous volume a good source of material for review of some of the activities in the field of cardiology

Heart and Coronary Arteries By Wallace A McAlpine MD New York, 19 5 Springer Verlag 223 pages Price $86.00

This is an outstanding *atlas of illustrations of the heart and coronary arteries* The figures are very clear and most of them are in color The author is to be praised for his work and this education The publishers have also done a magnificent job The illustrations and associated text and legends should not only interest surgeons, coronary angiographers and cardiologists, but trainees in all fields of cardiology as well This atlas is worth owning *as a reference book and for study* There are 1038 figures in the atlas and they are based on actual dissections of human hearts. Doctor McAlpine has produced a very useful atlas on the heart and coronary arteries The price $86.00 though high is readily appreciated with so many illustrations in color

Clinical Exercise Testing By Norman L Jones MD E J Moran Campbell MD Richard H T Edwards, BSc PhD and Denis C Robertson MD Philadelphia 19[illegible] W B Saunders Company 214 pages.

This book on clinical exercise testing should interest all doctors in view of the extensive interest in exercise stress testing in cardiology The authors summarize extremely succinctly in 214 pages (including the index) the clinical physiologic problems related to exercise testing They present very well in an organized and logical fashion the physiology of exercise and the associated physiologic changes and stress related to exercise. Oxygen consumption work performance methods, computer use normal standards and interpretations are among the many aspects clearly and succinctly presented This is an excellent book on the physiology of exercise The ECG changes associated with the treadmill exercise testing is not a part of this book Nevertheless those who employ treadmill testing in clinical cardiology will find this to be a valuable book.

Advances in Prostaglandin and Thromboxane Research volumes 1 and 2 Edited by Bengt Samuelsson and Rodolfo Paoletti, New York, 19 6 Raven Press, 506 pages

These two volumes contain most of the papers presented at a symposium on prostaglandins held in Florence Italy May 26 to 30 1975 During the conference the new term "thromboxane" was introduced to denote compounds derived from endoperoxides with an oxane ring structure These two volumes thoroughly review the important subject of prostaglandins These compounds are extremely important biologic substances which influence the metabolism and function of many life processes. The role of prostaglandins in pregnancy reproduction gastrointestinal function behavior of platelets nervous system physiology respiration cardiovascular system physiology and inflammation are among the many aspects of prostaglandin physiology and pharmacology presented The chemistry inhibitors receptors and other aspects of these interesting compounds are well presented It is fortunate to have available in these two valuable volumes such a wealth of information on prostaglandins potent agents which influence the health of man

Mechanisms of the Contraction of the Normal and Failing Heart, second edition By Eugene Braunwald MD John Ross, Jr MD and Edmund H Sonnenblick MD Boston 19 6 Little Brown & Company 417 pages.

This second edition on myocardial contraction and energetics reviews very effectively the present concepts of heart muscle contraction in normal and failing hearts After all the heart is the "power station" of the circulation This organ must be understood The relationship of ultrastructure to myocardial contraction and function is emphasized The hemodynamic studies of recent years are thoroughly reviewed and the references are extensive The authors have been directly involved in these problems for many years This is an authentic review of the normal and failing heart The book should interest all cardiologists and physiologists.

Advances in Pacemaker Technology Edited by M Schaldach and S Furman, New York, 19 5 Springer Verlag 504 pages

This volume represents the proceedings of an international symposium held in Erlangen Germany on September 26 and 27 1974 The sessions consisted of several papers on various subjects recorded as chapters in this book The six chapters are concerned respectively with principles and techniques of pacing clinical experience patient management longevity and pacemaker power sources and clinical experience with long life pacemakers The papers are clearly presented with the main emphasis on the clinical aspects of pacemaker applications The engineering phases are relatively minor even though this is volume 1 of *Engineering in Medicine* This is a very good publication which should interest all cardiologists and cardiac surgeons as well as all internists and general practitioners who see many patients with heart disease

regarding our article They have made a number of interesting observations

1 It is interesting that they have not seen calcification in children under the age of 15

2 We also recognize that some children have severe subvalvular pathology and that they may be suitable for open valvulotomy The findings on auscultation (softening of the first heart sound and the opening snap) and decreased valve cusp excursion with multiple leaflet echoes and thickened chordae on echocardiography suggest rigid valve cusps In these circumstances we now recommend open valvulotomy

3 We too have used the low profile Bjork Shiley valve but we still prefer the homograft if the valve ring is small

4 We must congratulate the authors on their [illegible] mortality rate

5 We too would like to treat all our patients with anticoagulants This is often technically impossible as they live in remote areas where adequate anticoagulant control cannot be undertaken

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American Heart Journal

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Editorial

Rehabilitation and length of hospitalization after acute myocardial infarction

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In 1912 Herrick wrote in his now famous article on acute coronary occlusion[1] "the importance of absolute rest in bed for several days is clear." And subsequently, as more knowledge about the pathology of myocardial infarction was accumulated, hospitalizations of 42 days and longer became the rule. Recently it was proposed that 7 days of hospitalization in "uncomplicated" acute myocardial infarction is sensible and feasible and it was recommended that a controlled clinical trial of such early hospital discharge is clinically and ethically desirable. The clinician can only be confused. Certainly our guiding principle for treatment must remain the individual patient's welfare when he is acutely ill and over the longer time and we must not confuse this important principle with expediency of any kind.

There has been considerable evidence to support the desirability of so called "early ambulation" in the treatment of patients with acute myocardial infarction. The American Heart Association has published a booklet supporting this concept, and for the most part we can agree that the routine described is sensible, effective, and well tolerated. Relatively rapid institution of rehabilitation procedures in patients who have suffered an acute myocardial infarction prevents or lessens physical deconditioning, has important psychological benefits, and does not appear to significantly alter acute mortality rate when compared to slower methods of ambulation.[3] It is likely that early ambulation decreases the frequency of thromboembolic phenomena from the legs in patients not on anticoagulant therapy.

The more rapid methods of ambulation should not be confused with the chair treatment introduced by Dr. Samuel Levine. This mode of treatment, as well as use of the bedside commode and the close-by bathroom, are not intrinsically related to accelerated rehabilitation programs and have been used by "conservative" physicians for a long time. Perhaps the earlier ambulation and rehabilitation programs are more appropriately characterized by "standing warm up exercises." In the uncomplicated myocardial infarction patient the physical routine at about 21 days (shortly before going home) would include lateral side bending with 2 pound weights, trunk twisting with 2 pound weights, touching toes from the sitting position, and walking up a flight of 10 stairs. Certainly these routines do not appear to be excessive and have much to commend them. However, they become quite cautious and timid compared to suggestions that uncomplicated myocardial infarction patients may go home after 7 hospital days. One must assume that "home" will not provide that degree of rest which we define in the hospital setting and that the oppor

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Books received

Quantitative Videoangiocardiography By R P van Wijk Brevingh Groningen The Netherlands 1975 Delft University Press 184 pages Price (Dutch florins) 49 75

Zwanzig Ubungen zur Einfuhrung in die Kardiologie By Professor Dr Med Walter Schweizer Berne Switzerland 1975 Hans Huber Publishers 325 pages Price 46 Swiss francs

Second International Adalat Symposium Edited by Wilh[illegible] Lochner Wolfgang Braasch and Gunther Kronberg, Ber[illegible] 1975 Springer Verlag 370 pages, Price $18 90.

Second Symposium International de Chirurgie Cardiaque Publié sous la direction de A Dequirot Paris, 19 6, Librairie Arnette Editeur 262 pages, Price 80 French francs.

Announcements

Clinical application of intra aortic balloon pump

On Nov 12 and 13 1976 Clinical Application of Intra Aortic Balloon Pump (IABP) (Second Annual Postgraduate Course) will be held in Miami Fla The program Director will be Hooshang Bolooki M D F R C S (C) It is sponsored by the Division of Thoracic and Cardiovascular Surgery and Cardiology Department of Medicine in cooperation with the Heart Association of Greater Miami The course is A M A accredited

For further information contact Division of Continuing Medical Education University of Miami School of Medicine P O Box 520875 Miami Fla 33152

American Heart Association/Virginia Affiliate

The American Heart Association/Virginia Affiliate scientific sessions will be held on April 22 and 23 1977 at the 1776 Inn Williamsburg Va

For further details contact American Heart Association Virginia Affiliate P O Box 12365 Richmond Va [illegible] Telephone (804) 643 7591

Pediatric and adolescent echocardiography course

Pediatric and adolescent echocardiography course—update 76 will be presented on Nov 13 and 14 19 6 (the two days preceding the American Heart Association meeting) in Miami Beach Fla The course ■ sponsored by the American Society of Echocardiography and the Postgraduate Educational Division of H E L P and is approved for Category I continuing education credit by the American Medical Association

Further information may be obtained from course director Stanley J Goldberg M D The University of Arizona 1501 N Campbell Tucson Ariz 85724 Telephone (602) 882 6[illegible]

...linical course of primary myocardial isease in infants and children

...onald D Greenwood M D
...lexander S Nadas M D
...onald C Fyler M D
...oston, Mass

...nce the initial clinical description and categori...ation of primary myocardial disease[1] (PMD) our ...nowledge of disease processes and congenital de...ects producing myocardial disease has greatly ...ncreased and allows a more detailed classifica...on (Table I) As techniques for elucidating ...tiologies have become practical patients have ...oved from the primary category to specific ...auses in the secondary category

The patient in whom clinical and laboratory ...valuations still produce no etiology remains ...n the group presently termed PMD This in...ludes three pathologic proved entities—idio...athic myocarditis nonobstructive cardiomyo...athy (NOCM) and endocardial fibroelastosis ...EFE) and a fourth category of patients in whom ...athology could not be determined including ...umors and those who died without post...mortem examinations This communication re...iews the course prognosis and differentiating ...eatures in this population from a 30 year experi...ence at our institution.

Materials and methods

The diagnostic files in the record room the Cardiology Department and the Cardiac Regis...try of the Children s Hospital Medical Center were searched for patients admitted with the diagnosis of myocardial disease between January 1945 and April 1974 Charts were reviewed as were the chest roentgenograms electrocardio...grams (ECG) vectorcardiograms catheterization data and postmortem material when available Patients with either primary obstructive (idio...pathic hypertrophic subaortic stenosis) or second...ary myocardial disease were excluded from this study (Table I)

The diagnosis of PMD in 161 patients was based on autopsy in 41 catheterization in 48 and clincal data alone in 71 According to previous definition[1] all patients had (1) cardiac enlarge...ment by x ray, (2) ST T changes on ECG (3) no murmurs louder than Grade 3/6, (4) no blood pressure gradient between upper and lower extremity Clincial observations were available in all Reasonable effort was always made to ex...clude known etiologies although muscle biopsies isuprel administration at catheterization viral titers or cultures were not performed consis...tently

ECG evidence of hypertrophy for atria and ventricles was based on published standards Cardiac enlargement was designated as present when the cardiothoracic ratio exceeded 0 50 Vectorcardiographic criteria of abnormality[3] and left ventricular volume determinations,[4] accord...ing to Simpson s rule were based on standards established in this department

During the course of the disease after the initial evaluation the cardiac status was followed periodically by clinical and laboratory examina...tions and classified into three groups Those who lost all clinical evidence of heart disease were designated as recovered Those with symptomatic or clinical and laboratory evidence of heart dis...ease were labeled as residual A final category included those who died

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Reprint requests, Ronald D Greenwood, M D D...partm...nt of Cardi...ology Children s Hospital Medical Ce...te... 300 Longwood A...nue, Boston, Massachusetts 02115.

tunity for graded rehabilitation will be sacrificed

There is no question that most dangerous complications of acute myocardial infarction occur early Programs of rehabilitation recognize this and do not particularly address themselves to the first 4 or 5 days after the acute insult Acute mortality statistics are not influenced by rehabilitation programs, and this is not surprising However, in the treatment of acute myocardial infarction we must also give attention to considerations other than the factor of acute mortality

During the stage of removal of necrotic muscle fibers resultant from acute ischemia there is demarcation between necrotic and viable muscle cells 'In this zone even though elsewhere there may be conglomerate masses of infarcted muscle characteristically there is alternation between small masses of viable muscle and areas of infarction [4] Thus it is characteristic with acute myocardial infarction that there is an area of ischemia of variable size and there is some evidence that such areas of ischemia may persist for considerable time [5] Removal of the necrotic fibers sometimes continues for weeks [4] but scar formation is seen *at the beginning* of the third week Usually most of the necrotic tissue is removed by the fourth week, and the scar development continues In a noteworthy editorial Blumgart and Zoll [6] emphasized the slow rate of development of collateral vessels after sudden coronary occlusion These authors stated The slow development of these channels as well as of the inflammatory reaction to necrosis emphasize the importance of rest and reduced activity for many weeks after acute myocardial infarction contrary to the current tendency to early ambulation The author and his co workers [7] have seen strikingly delayed healing processes in one experimental condition which may sometimes be pertinent to healing of myocardial infarctions in man

Early ambulation programs clearly make both patients and physicians feel better sooner But the long term value to the patient still must be considered as unproved in the area of our greatest concern, the effective and maximal healing of an injured muscle with the survival of as much of that muscle as possible After acute myocardial infarction it is desirable to protect the ischemic myocardium and to facilitate collateral vessel formation The processes of healing and collateral vessel growth may be altered unfavorably if our concern with deconditioning becomes excessive

It remains to be established whether there is any value to early ambulation of patients after acute myocardial infarction other than the psychologic benefit However, there are sensible programs oriented to around three weeks of hospitalization that offer a reasonable middle route to follow in the light of our present knowledge, understanding that it remains possible that earlier ambulation is associated with more frequent late complications Such complications would include higher rates of recurrent infarction, congestive heart failure, angina pectoris ventricular aneurysm, mural thrombi, and ventricular dysrhythmias Such plans as those which would markedly shorten the period of hospitalization may accomplish certain cost benefits, but they would in effect sacrifice the carefully developed programs of rehabilitation after acute myocardial infarction One would hope that evaluations of the safety of markedly abbreviated hospitalizations would be confined to an investigative setting in which long term complications could be adequately assessed

REFERENCES

1 Herrick J B Clinical features of sudden obstruction of the coronary arteries J A M A 59 2015 1912
2 McNeer J F Wallace A G Wagner G S Starmer C F and Rosati R A The course of acute myocardial infarction Feasibility of early discharge of the uncomplicated patient Circulation 51 410 1975
3 Wenger N D Coronary care Rehabilitation after myocardial infarction American Heart Association New York 1973
4 Lynch R P and Edwards J E Pathology of coronary atherosclerosis and its complications *in* Hurst J W and Logue R B editors The heart McGraw Hill Book Co New York 1966 pages 658 669
5 Pick R Miller A J and Glick G Myocardial pathology after cardiac venous and lymph flow obstruction in the dog Am Heart J 87 627 1974
6 Blumgart H L and Zoll P M Clinical pathologic correlations in coronary artery disease Circulation 47 1139 1973
7 Kline I K Miller A J Pick R and Katz L N The effects of chronic impairment of cardiac lymph flow on myocardial reactions after coronary artery ligation in dogs Am Heart J 68 515 1964

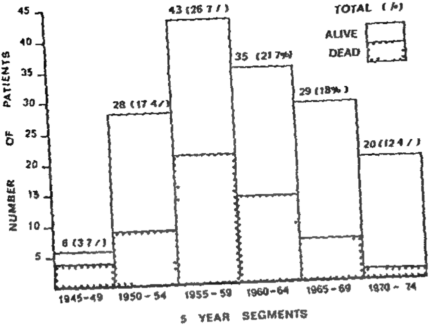


Fig 1 Number of cases of primary myocardial disease and deaths in 5 year periods

Table II Age of onset of symptoms in primary myocardial disease according to clinical outcome

Category	No	Per cent		Age at first encounter			
				≤ 1 mo	2 mo 1 yr	13 mo 2 yr	> 2 yr
Resolved	43	27		4	16	7	16
Residual	61	38					
Endocardial fibroelastosis	2		1 2	0	2	0	0
Cardiomyopathy*	2		1 2	0	0	1	1
Not known	57		35 4	5	25	7	20
Dead	57	3.					
Endocardial fibroelastosis	18		11 2	1	11	[illegible]	6
Myocarditis	13		8 1	5	5	1	2
Cardiomyopathy	10		6 2	1	1	-	6
Not known	16		9 9	2	2	1	11
Total	161	100		18	62	19	62

*Familial

included gastrointestinal complaints (vomiting abdominal pain) fever isolated arrhythmia heart murmur and fatigue Symptoms were present prior to entering the hospital for 24 hours or less in 45 (28 per cent) although a number of additional patients or parents could remember a recent illness which could not be clearly related

Physical examination Some evidence of infection including fever was present at initial encounter in 46 (28 5 per cent) of the total group including 69 per cent of those who died with myocarditis and an appreciable though smaller percentage of the others (Table III) Fever (noted as a rectal temperature of 101 F or more) was noted in 24 (15 per cent) Ten of 24 with fever died and eight of them were proved post mortem *not* to have myocarditis Three of the 161 patients were seen with a clear picture of central nervous system infection—encephalitis and/or meningitis Two died 1 and 2 days after initial encounter whereas one had *no* evidence of disease one 4/12 years later No virus could be recovered from these patients

The heart sounds on initial examination were noted to be muffled in only 12 patients (8 per cent) A third heart sound was detected in 58 (36

Table I Classification of myocardial disease

Primary
- Myocarditis (idiopathic)
  - Nonobstructive cardiomyopathy (isolated or familial)
  - Endocardial fibroelastosis (isolated or familial)
  - Unclassifiable (survivors and dead without postmortem)

Secondary
- Generalized disease
  - Collagen disease (rheumatic fever juvenile rheumatoid arthritis systemic lupus erythematosus periarteritis nodosa dermatomyositis scleroderma)
  - Systemic hypertension
  - Neuromuscular (Friedrich s ataxia muscular dystrophy)
  - Glycogenosis (Pompe s disease)
  - Acute glomerulonephritis
  - Other (Hurler Hunter thalassemia nutritional)
- Congenital malformations of the heart
  - Anomalous coronary artery
  - Medial necrosis coronary artery
  - Dysfunction associated with congenital heart disease (left ventricular dysfunction associated with tetralogy atrial septal defect etc)
  - Endocardial fibroelastosis associated with congenital heart disease (coarctation aortic stenosis etc)
  - Neoplasms (local or generalized) (rhabdomyoma tuberous sclerosis)
- Infections (proved)
  - Bacterial (diphtheria)
  - Viral (coxsackie mononucleosis rubella measles mumps varicella variola poliomyelitis rabies other)
  - Rickettsial (typhus)
  - Protozoal (visceral larva migrans histoplasmosis toxoplasmosis)
- Damage
  - Irradiation
  - Adriamycin
  - Lead intoxication
  - Scorpion bite

Not included is obstructive cardiomyopathy (idiopathic hypertrophic subaortic stenosis) which is better classified with aortic stenosis

Results

Incidence and general overview A total of 161 infants and children with primary nonobstructive myocardial disease were detected The number of patients with the diagnosis of PMD and their mortality rate in 5 year blocks are presented in Fig 1 After an initial increase in cases concomitant with the formation of the Cardiology Department in 1949 the incidence of myocardial disease has declined in recent years as has the mortality rate, although the total congenital heart disease admissions and numbers catheterized at this hospital have increased over the same years The proportions by diagnosis are seen in the same five year blocks in Fig 2 The inciden of EFE has been declining in recent years an most children in recent years have the familia variety (60 per cent in the last 15 years a compared to 20 per cent for the first 15 years o this study) The incidence of myocarditis and my opathy have not varied significantly except for a disproportionately high percentage of myocar ditis between 1955 and 1959 These variances may be related solely to mortality rates In Table II patients were divided according to clinical course into those who (1) recovered completely (resolved) (27 per cent), (2) continued to have residual disease (38 per cent) or (3) died (35 per cent) this latter category is then comprised of those with postmortem proved EFE NOCM (idiopathic nonobstructive myopathy with no evidence of inflammation or of endocardial sclero sis) and myocarditis and those who died without autopsy

Clinical presentation No clear clinical differ entiation is possible between the various etiolo gies of PMD, therefore the group is discussed as a whole Serious associated extracardiac anomalies or syndrome complexes were noted in seven (4 per cent) and included two with Noonan syndrome and one each with blindness, supernumerary digit congenital glaucoma microcephaly, and a connective tissue disorder (*form fruste* Marfan with a deleted short arm of an acrocentric chromosome) Thirteen (8 1 per cent) had definite family history of heart disease and included EFE in eight NOCM in four and structural congenital heart disease in one Another eight (5 per cent) had possible positive histories (unknown heart disease causing death) Two other children with inherited illnesses had clear evidence of myocar ditis (hemophilia A cystic fibrosis) The sex inci dence was equal (82 male 79 female)

The outcome and age at onset of these patients are presented in Table II The average age at on set was 3 7 years and ranged from 1 day to 1? years Approximately one half of the patients (?0/ 161) were under 1 year of age when first seen Only one of 20 with EFE was seen first under 1 month of age

The major presenting symptom in 105 patients (65 per cent) was respiratory distress, 14 (9 per cent) were first seen with neurologic manifesta tions (seizure syncope, lethargy) and 13 (9 per cent) were noted to have solitary cardiac enlarge ment Other less common initial symptoms

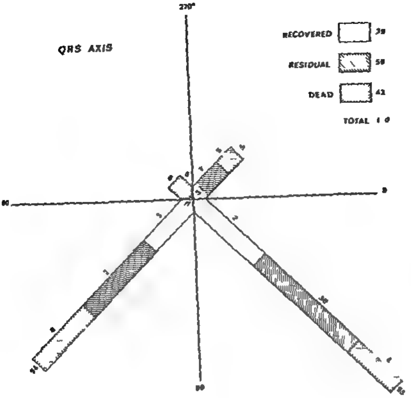


Fig 3 Distribution of mean frontal plane QRS axis

initial encounter (Table IV) Among the dead the majority particularly those with myocarditis and cardiomyopathy had no left ventricular hypertrophy As expected most but surely not all patients with proved FFE had significant left ventricular hypertrophy An appreciable number of patients who recovered completely had significant, even marked left ventricular hypertrophy initially Only seven patients had right ventricular hypertrophy on the initial ECG two of these recovered, four were left with heart disease and only one died There were no patients with EFE or myocarditis with right ventricular hypertrophy in the series About one half of the patients (78) had left atrial right atrial or combined atrial hypertrophy

Five patients exhibited QS complexes characteristic of myocardial infarction Four were in the left chest leads and one in Leads I and aV_L Two of these recovered with residual heart disease the QS pattern disappeared in one of these Three died within days or months after they first became sick and none of these had anomalous coronary artery

Twenty six of (16 per cent of the total series) exhibited arrhythmias sometime during the

Table IV Left ventricular hypertrophy at initial encounter

Category	*LVH*	*NO LVH*
Resolved (41)	15	26
Residual (61)	33	28
Dead (48)	19	29
Endocardial fibroelastosis	10	4
Myocarditis	1	7
Cardiomyopathy	3	7
Not known	5	11
Total (150)	67	83
	(45%)	(55%)

Table V Arrhythmias in patients with myocardial disease

Disease	*No*
Wolff Parkinson White syndrome	4
Ventricular (premature ventricular contraction, bigeminy ventricular tachycardia)	11
Supraventricular (tachycardia)	8
Conduction disturbance (second-degree A V block, A V dissociation)	3
Total	26

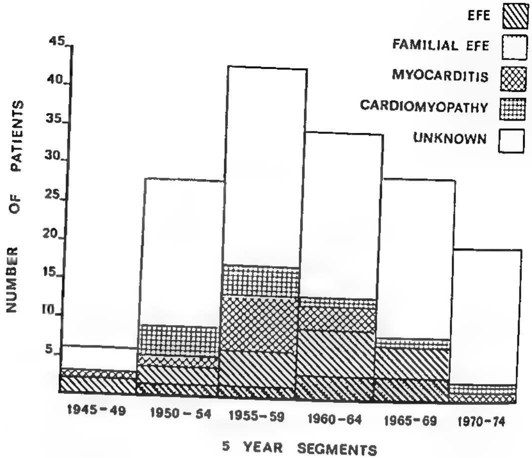


Fig 2 Types of primary myocardial disease in 5 year periods

Table III Evidence of infectious disease

Category	No		Evidence of infection	Per cent
Recovered	43		15	34 9
Residual	61			
Endocardial fibroelastosis		2	0	0
Cardiomyopathy		2	1	50 0
Not known		57	9	15 8
Dead	57			
Endocardial fibroelastosis		18	5	27 8
Myocarditis		13	10	76 9
Cardiomyopathy		10	4	40 0
Not known		16	2	12 5
Total	161		46	28 6

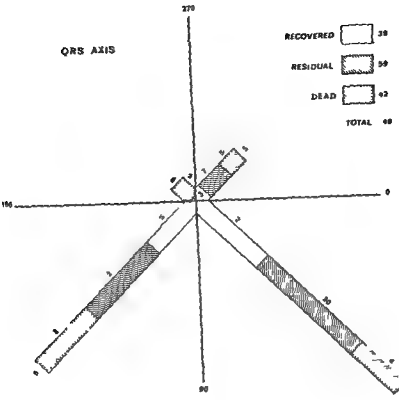
per cent), a fourth sound or a summation gallop was heard in eight Only six had systolic murmurs of Grade 3/6 intensity, two others had diastolic murmurs Hepatomegaly (greater than 3 cm palpable below the right costal margin) was present in 106 (65 per cent) patients

Clinical laboratory Erythrocyte sedimentation rate, white blood count and enzymes (serum glutamic oxalacetic transaminase serum glutamic pyruvic transaminase, lactic dehydrogenase) were frequently elevated but did not prove to be of value in determining etiology or clinical course Heterophile antibody titer, antistreptolysin O titer lupus erythematosus preparations, cultures of blood, urine throat sputum stool, viral titers and muscle biopsies when done were normal or negative

Chest roentgenogram On initial x ray all had cardiac enlargement which was usually quite marked and generalized although some revealed characteristic left ventricular contours and others were globular in shape Fifty five of 153 (36 per cent) had pulmonary venous congestion and were associated with definite infiltrate in a small number One half (26/55) of those with pulmonary congestion died whereas only 1/4 (23/95) of those without such died

ECG All showed evidences of ST T segment abnormality—usually flattening and inversion in Leads I and aV_L, and over the left precordium. The distribution of mean frontal plane axes is presented in Fig 3 It may be seen that 85 per cent of the patients had inferior frontal plane axes—half of them being normal, the other half having right axis deviation

Slightly less than one half of the patients (45 per cent) had left ventricular hypertrophy at



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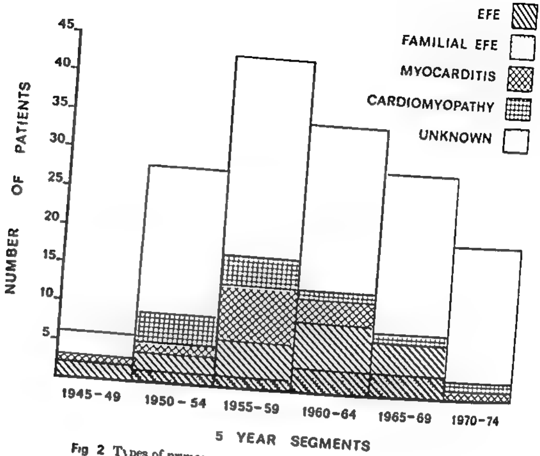

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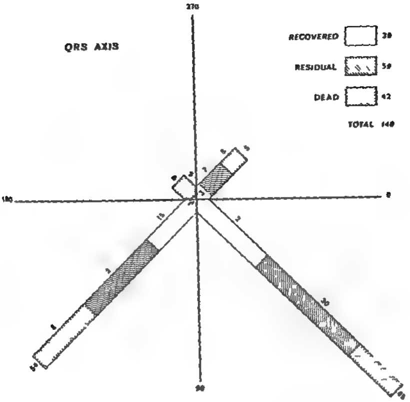

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Table VI Deterioration of cardiac function in a patient with primary myocardial disease

Age (yr)	Time after diagnosis (yr)	Catheterization data			
		Cardiac index (L/min/M²)	Pulmonary artery pressure (mm Hg mean)	Pulmonary capillary pressure (mm Hg mean)	Right atrium pressure (mm Hg me[an])
9 11/12	1	3 8	22	12	2
20 7/12	11 1/2	3 6	26	14	5
23 6/12	14 1/2	1 4	45	31	28

course of the disease 23 of these at initial encounter The types of arrhythmias are seen in Table V Seven of the 26 patients with arrhyth mias now show no evidence of cardiac disease nine are alive with heart disease (including six with arrhythmias) and 10 are dead Patients with myocarditis were seen no more frequently with arrhythmias than any other group

Vectorcardiograms Vectorcardiograms were available in 27 patients 13 (48 per cent) had left maximal spatial voltages consistent with left ventricular hypertrophy The majority (23) had counterclockwise horizontal loops four had superior frontal loops Clear anterior or lateral infarct or absent initial anterior forces of depolar ization were seen in 16 of 21 patients with vector cardiograms available for detailed examination Two patients one with anterior and one with lateral infarct had repeated vectors over a period of 1 and 7 months and showed mild improvement in infarct pattern

Cardiac catheterizations Sixty six cardiac catheterizations were performed in 56 patients with one death this occurred in 1964 due to perforation in a 5 day old patient with proved myocarditis

Initial (56) Ten of these studies showed no hemodynamic abnormalities only five of these showed at last evaluation some residual abnor mal clinical findings The results of all 56 studies may be summarized briefly as follows Systemic artery saturations were normal (91 to 98 per cent) in all There were only six patients with mean pulmonary artery pressure greater than 30 mm Hg (range 34 to 50) three of these presently have residual disease and three died Among the 14 with pulmonary artery mean pressures from 20 to 29 only two recovered completely and seven died whereas among the 35 with pressures less than 20 mm Hg nine now have no evidence of heart disease and five are dead Cardiac index va[ried] widely but was less than 3 L per minute [per] square meter in only 13 Eight of these died [and] only one recovered completely Among [the] patients with cardiac index greater than th[ree] nine recovered and only seven died Pulmona[ry] capillary wedge pressure, or left ventricular en[d] diastolic pressure was greater than 15 in [nine] instances three of these patients recovere[d] completely and six died Of the remaining [] patients with pulmonary capillary wedge pressu[re] of 15 or less seven recovered and eight die[d] Mitral regurgitation was present (angiographi cally) in nine patients but was mild to moderat[e] in all seven of them have residual disease and two are dead

Repeat (10) Seven patients were recatheterized (10 catheterizations) from 6 months to 19 year[s] after initial encounter Cardiac index was three or less on only two occasions (1 4 and 3 0) Mean pulmonary artery pressure ranged from nine to 45 and was above 30 in only one instance pulmonary capillary wedge pressure ranged from 4 to 31 and was above 15 in only one instance Data from one patient with familial NOCM who underwent repeat studies are shown in Table VI and deterioration of cardiac function is evident This young man received a heart transplant [] months after the last catheterization and [] months post transplantation is doing very well

Volume determinations Biplane angiogram[s] were adequate for left ventricular volume deter minations (end diastolic volume end systolic volume ejection fraction and mass of left ventri cle) in 14 patients two had volume determina tions performed on a second catheterization also Results were normal in four patients all of whom recovered Among the 10 patients with abnormal studies only two recovered and eight had residual disease Residual disease resulted in all patie[nts]

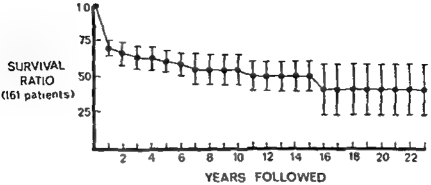

Fig 4 Cumulative survival of all patients with primary myocardial disease The survival ratio is a representation of (No alive/No followed) Standard error is indicated by broken lines

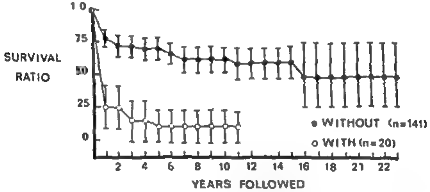

Fig 5 Cumulative survival of patients with and without endocardial fibroelastosis The survival ratio is a representation of (No alive/No followed) Standard error is indicated by broken lines.

mass greater than 160 Gm /M² (normal 50 to 0) an end-diastolic volume of greater than 125 c/M² (normal 50 to 80) an ejection fraction ess than 0 3 or an end systolic volume greater han 90 c c /M² (normal 10 to 35)

Treatment Treatment included oxygen bed est antibiotics digitalis diuretics fluids and steroids. Digitalis in standard dosages was administered to 80 per cent of the patients toxicity occurred only in three Patients in whom digitalis was not administered included those with solitary cardiac enlargement and a few who died prior to institution of therapy Diuretics including thiazides mercurials furosemide and ethacrynic acid were administered in standard dosages to 40 per cent of the patients Steroids were administered to only 14 critically ill patients. Of these nine died two survived with residual disease and three recovered

Follow up A total of 161 patients have been followed for from 1 hour to 23 years after initial encounter with a mean of 41 months (median 14 months) Sixty five patients (40 per cent) were followed for 2 years or more (mean 9 3 years) there were 16 patients who were followed for 10 years or longer

Fifty seven (35 per cent) died from 1 hour to 15 years after first seen (median 2 months mean 13 months) 32 (56 per cent) died within the first month and 44 (77 per cent) within the first year of their illness All patients dead with myocarditis died within the first year and 12 of these 13 died during the first month of their illness There were only three with EFE who died beyond 1 year of recognition of heart disease By contrast in those with myopathy and unknown PMD death could occur any time after the first symptoms The great majority of those who died had intractable failure cardiac enlargement and ST T wave changes less than 1/2 (24/57) had left ventricular hypertrophy

The 104 patients who are alive have been followed for an average of 55 months (median 36 months) Forty three have entirely recovered and 61 have residual cardiac disease including cardiac enlargement in 51 chronic congestive heart

Table VI Deterioration of cardiac function in a patient with primary myocardial disease

		Catheterization data			
Age (yr)	*Time after diagnosis (yr)*	*Cardiac index (L/min/M²)*	*Pulmonary artery pressure (mm Hg mean)*	*Pulmonary capillary pressure (mm Hg mean)*	*Right atrium pressure (mm Hg mean)*
[redacted] 11/12	1	3 8	22	12	2
20 7/12	11 1/2	3 6	26	14	5
23 6/12	14 1/2	1 4	45	31	23

course of the disease 23 of these at initial encounter The types of arrhythmias are seen in Table V Seven of the 26 patients with arrhythmias now show no evidence of cardiac disease nine are alive with heart disease (including six with arrhythmias) and 10 are dead Patients with myocarditis were seen no more frequently with arrhythmias than any other group

Vectorcardiograms Vectorcardiograms were available in 27 patients 13 (48 per cent) had left maximal spatial voltages consistent with left ventricular hypertrophy The majority (23) had counterclockwise horizontal loops four had superior frontal loops Clear anterior or lateral infarct or absent initial anterior forces of depolarization were seen in 16 of 21 patients with vectorcardiograms available for detailed examination Two patients one with anterior and one with lateral infarct had repeated vectors over a period of 1 and 7 months and showed mild improvement in infarct pattern

Cardiac catheterizations Sixty six cardiac catheterizations were performed in 56 patients with one death this occurred in 1964 due to perforation in a 5 day old patient with proved myocarditis

Initial (56) Ten of these studies showed no hemodynamic abnormalities only five of these showed at last evaluation some residual abnormal clinical findings The results of all 56 studies may be summarized briefly as follows Systemic artery saturations were normal (91 to 98 per cent) in all There were only six patients with mean pulmonary artery pressure greater than 30 mm Hg (range 34 to 50) three of these presently have residual disease and three died Among the 14 with pulmonary artery mean pressures from 20 to 29 only two recovered completely and seven died whereas among the 35 with pressures less than 20 mm Hg, nine now have no [redacted]vidence of heart disease and five are dead Cardiac index varied widely but was less than 3 L per minute per square meter in only 13 Eight of these died and only one recovered completely Among 4? patients with cardiac index greater than three nine recovered and only seven died Pulmonary capillary wedge pressure or left ventricular end diastolic pressure was greater than 15 in 15 instances three of these patients recovered completely and six died Of the remaining 39 patients with pulmonary capillary wedge pressure of 15 or less, seven recovered and eight died Mitral regurgitation was present (angiographically) in nine patients but was mild to moderate in all seven of them have residual disease and two are dead

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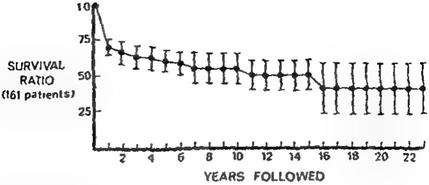

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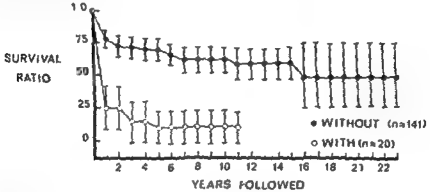

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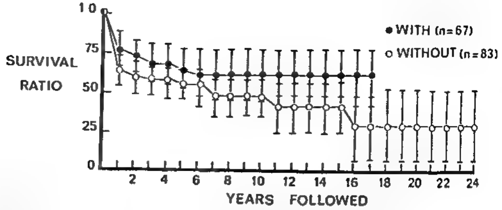

Fig 6 Cumulative survival in patients with and without heart failure at initial encounter The survival ratio is a representation of (No alive/No followed) Standard error is indicated by broken lines.

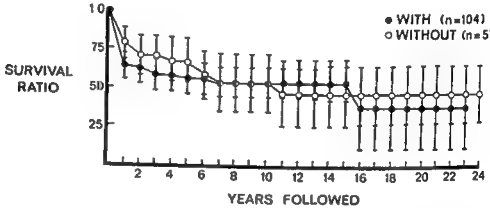

Fig 7 Cumulative survival of patients with and without left ventricular hypertrophy at initial encounter The survival ratio is a representation of (No alive/No followed) Standard error is indicated by broken lines.

failure in 21, persistent ST T wave changes in 51 and left ventricular hypertrophy in 37 Three patients experienced documented cerebrovascular accidents during their course no instance of pulmonary emboli was detected

A composite life table including all patients with PMD is seen in Fig 4 After a high early mortality rate attrition is unusual one half of those followed to 15 years were alive The same presentation (Fig 5) is applied to those with and without proved EFE, showing the markedly high mortality rate in the former group and in part—but not wholly—explained by the definition of the diagnosis Patients with or without left ventricular hypertrophy at initial encounter are seen in Fig 6 and those with and without congestive heart failure are represented in Fig 7 Clearly these two factors are not helpful in determining the prognosis

Discussion

Definition PMD as defined in the present report represents a spectrum of patients with cardiac muscle dysfunction Idiopathic myocarditis NOCM, and EFE are descriptive te applied to explain certain pathologic aspects the spectrum of disease Although particular cl ical findings tend to make one or the other these categories more likely, these disea es similar and overlap in method of presentation

Clinical comments An infarct pattern in ECG may be seen without the presence coronary artery disease as has been previou reported[6,7] and is well established in adult Any patient with characteristic anterolate myocardial infarct however, must be cathet ized to rule out anomalous left coronary arte When vectorcardiograms are employed, depola zation abnormalities in the horizontal loop a more obvious evidence of infarct are frequent seen The absence of any left to right spread activation across the intraventricular septum h been noted in adults[10] Adult vectorcardiogra have been divided[11] into inferior or super frontal plane axes with a significant percenta in each group yet it is uncommon in children have a superiorly oriented frontal loop In ad tion, other common disturbances in adults[1] l

Table VII Clinical pattern in anatomic proved types of primary myocardial disease

Anatomic diagnosis	Clinical: Presentation under 1 mo	Clinical: Presence of heart failure	Clinical: Presence of infection	X ray: Cardiomegaly	X ray: Vascular congestion	ECG: STT changes	ECG: Left ventricular hypertrophy	Catheterization cardiac index under 3 L/min/M
EFE	Rare	3/4	1/3	All	1/2	All	2/3	All
Myocarditis	1/2	2/3	3/4	All	1/2	All	Rare	0
NOCM	Rare	3/4	1/2	All	1/2	All	1/3	1/2

...s seen but few catheterized

d right bundle branch block are uncommon in ...ildren Catheterization excludes anatomic ...ses for the findings and often reveals a poorly ...ntractile left ventricle with elevated left ...ntricular end diastolic pressure in about one ...ird, elevated pulmonary artery pressure in a ...aller number and occasionally low cardiac ...dex. The degree of abnormality varies with ...erity Other studies substantiate these find...gs.[1] Our patients were not subjected to exer...se, which would be expected to accentuate ...normal cardiac function and other abnormali...s not seen at rest Left ventricular volume ...terminations are often abnormal

Treatment Digitalis used cautiously to avoid ...oxicity [1] and diuretics may be lifesaving ...bedrest [1] antibiotics proper fluid manage...ment and other supportive measures are also ...crucial. Infants and children with congestive ...heart failure often respond dramatically to these ...measures Some children however do not ...improve steroids administered to the more ...severely ill did not alter the outcome Cortico...steroid therapy for PMD is highly controver...sial. Arrhythmias are treated with standard ...antiarrhythmic agents Valve replacement has ...been suggested for those patients with aortic or ...mitral incompetence severe valvar lesions were ...not present in this series Cardiac transplantation ...remains one potential mode of therapy for those ...with severe chronic PMD before this is utilized ...except as a last resort the difficulties with rejec...tion must be resolved

Course One third of the patients die most ...during the first months of illness another third ...continues to exhibit some evidence of heart ...disease approximately a third will return entirely ...to normal Patients with residual lesions have an ...uncertain future It has been noted that in many infants and children who survive the initial episode recovery is nearly complete although ECG and roentgenographic changes may require years to resolve [3] whereas the prognosis for the infant with idiopathic myocarditis with a short history in severe failure has been reported to be poor In adults persistent cardiomegaly gallop rhythm intraventricular block and repeated heart failure indicate a grave prognosis[5]

Some factors when present at onset significantly ($p < 0.01$) predict a *more ominous* outcome Included are pulmonary vascular congestion (26 [dead] out of 55 vs 23 [dead] out of 98 without this finding) cardiac index less than 3 L/min/M (8 dead of 13 vs 7 of 42) and *northwest axis deviation* (5 dead of 6 vs 37 of 134) The presence of heart failure arrhythmia left ventricular hypertrophy or onset as a neonate do not appear to significantly alter the outcome

Etiology No etiology is known at present for EFE or NOCM although familial occurrence and much discussion of etiology have taken place Although myocarditis is associated with multiple etiologic agents most myocarditides remain of unknown etiology[1] As serologic examinations and techniques for isolation of viruses become more available much that was said to be idiopathic may be recognized to be due to specific viral infections

Differential diagnosis Patients with PMD who have recovered completely are often critically ill when first seen and cannot be differentiated from the groups resulting in residual or terminal disease Although left ventricular hypertrophy is seen more often in postmortem proved EFE than in myocarditis overlap occurs and patients losing all evidence of cardiac disease certainly had left ventricular hypertrophy This suggests that PMD

is a spectrum and we are not seeing three different diseases but the response of cardiac muscle to injury The high incidence of left ventricular hypertrophy[7, 1, 43, 81, 81] and earlier presentation[1, 8] are helpful in diagnosis of EFE although previous reports and this series remind us that apparent myocarditis may be seen with left ventricular hypertrophy[3, 4] and that it (with no evidence of Coxsackie virus) may be present in neonates Based on postmortem proved cases only anatomic type of PMD and the typical clinical presentation of each are seen in Table VII

Idiopathic hypertrophic subaortic stenosis or obstructive cardiomyopathy appears to belong in the spectrum of myocardial disease although in this series of patients we have attempted to exclude it It does exist in kindred with NOCM[81] and has developed in some patients in our institution originally diagnosed as nonobstructive cardiomyopathy There is some evidence in adults[84] that NOCM is an acquired disease

Evaluation of the hypothesis that EFE may resolve is not possible from this study because EFE was defined by postmortem analysis or by family history only Although others suggest[85] that patients with EFE do well clinically no patient whom we have identified as having EFE prior to death (familial cases) has deviated from a course of progressive deterioration

One should pursue an exact etiologic diagnosis as far as possible The exclusion of known causes (Table I) allows the diagnosis of PMD In this group, although at present it is of no proved therapeutic application an attempt should be made to characterize the endomyocardial manifestations of disease Endomyocardial biopsy may be of some value[4] in this regard although our experience so far has not been fruitful

Summary

A total of 161 infants and children ranging in age from 1 day to 17 years at initial encounter (mean, 3 7 years), was seen over a 30 year period with primary myocardial disease (idiopathic myocarditis nonobstructive cardiomyopathy endocardial fibroelastosis and an anatomically unknown category) These patients were observed from 1 hour to 23 years after initial encounter and cardiac disease has resolved in 27 per cent resulted in death in 35 per cent, and continues in 38 per cent The majority were first referred to us with congestive heart failure, all exhibited ST changes and cardiomegaly, 67 of 150 had ventricular hypertrophy, 23 of 151 arrhythm and 55 of 153 pulmonary vascular congesti Initial ventricular depolarization abnormali were very frequent Significant clinical predict of fatal outcome included pulmonary vascu congestion, "northwest" axis deviation and cardiac index less than three L/min/M² Dea occurred during the first year after ini encounter in 44 of 57 who died, and in all 13 wi proved myocarditis Primary myocardial disea is a serious disease of infancy and childhoo resulting in death or residual cardiac disease i three fourths of those affected

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REFERENCES

1 Rosenbaum H D Nadas A S and Neuhauser E B D Primary myocardial disease in infancy a childhood Am J Dis. Child 86 98 1953.
2 Guntheroth W G Pediatric electrocardiography Phila delphia 1965 W B Saunders Company
3 Ellison R C and Restieaux N J Vectorcardiograph in congenital heart disease Philadelphia 19 2, W B Saunders Company
4 LaFarge C G and Keane J F Unpublished data, personal communication 1974
5 Nadas A S and Fyler D C Pediatric cardiolog Philadelphia 1972 W B Saunders Company
6 Gross H Rubin J L and Dardik I Abnormal Q waves in a child with myocarditis N Y State J Med 67 283 1967
7 Lambert, E C and Vlad P Primary endomyocardial disease Pediatr Clin North Am 5 1057 1958
8 Hamby R I and Raia F Electrocardiographic aspe of primary myocardial disease in 60 patients, Am Heart J 76 316 1968
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10 Flowers N C and Horan L G Electrocardiographic and vectorcardiographic features of myocardial disease, in Fowler N D editor Myocardial diseases, New York 1973 Grune & Stratton Inc p 181
11 Hamby R I and Raia R Vectorcardiographic a pect of primary myocardial disease in 50 patients Am Heart J 70 301 1968
12 Moller J N Lucas R V Adams P Anderson R C Jorgens J and Edwards J E Endocardial fibroelasto sis A clinical and anatomic study of 47 patients wit emphasis on its relationship to mitral insufficien Circulation 30 759 1964
13 McLaughlin T G Schiebler G L and Krovetz L J Hemodynamic findings in children with endocardial fibroelastosis Am Heart J 75 162 1968
14 Goodwin J F Cardiac function in primary myocardial disorders Part I Br Med J 1 1527 1964
15 Goodwin J F Cardiac function in primary myocardial disorders. Part II Br Med J 1 1595 1964

Pietras, R. J Meadows, W R Fort M and Sharp J T Hemodynamic alterations in idiopathic myocardiopathy including cineangiography from the left heart chambers, Am. J Cardiol 16 6 2 1965

Yu, N Schreiner B F., Cohen J and Murphy W Idiopathic cardiomyopathy A study of left ventricular function and pulmonary circulation in 15 patients, Am Heart J 71 330 1966

Hamby R. I Primary myocardial disease Medicine 49 55 1970

Dye, C L., Genovese P D Daly W J and Behnke R. H. Primary myocardial disease Part II Hemodynamic alterations, Ann Intern Med 58 442 1963

Lynfield, J Gasul, B M., Luan L. L and Dillon R F Right and left heart catheterizations and angiocardiographic findings in idiopathic cardiac hypertrophy with endocardial fibroelastosis, Circulation 21 386 1960

Fowler N O Gueron M and Rowlands D T Primary myocardial disease Circulation 23 498 1961

Graham, T P Jr Sarmakani, M W Canent R V Capp M. P and Spach, M S Characterization of left heart volumes and mass in normal children and in infants with intrinsic myocardial disease Circulation 38 876, 1968

3. Harvey W P Comments on symposium Circulation 32 857 1965

4. Burch, G E., Walsh, J J Ferrans, V J and Hibbs Q Prolonged bed rest in the treatment of the dilated heart Circulation 32 852, 1965

5. Tilles, J G Elson S H Shaka J A Abelmann W Lerner A. M and Finland M Effects of exercise on coxsackie A9 myocarditis in mice Proc Soc Exp Biol Med. 117 777 1964

26. Ainger L. E Somerall, B Fitch C W Lane N K and Harper W H. Corticosteroid therapy of acute nonrheumatic myocarditis, Am J Dis Child 100 737 1960

Segal, J P Harvey W P and Gurel T Diagnosis and treatment of primary myocardial disease Circulation 32 837 1965

28. Mattingly J W The clinical concept of primary myocardial disease Circulation 32 845 1965

29. Ainger L. E Acute aseptic myocarditis corticosteroid therapy J Pediatr 64 16 1964

30. Aber L. P and Jones, W W Corticotropin and corticosteroids in the management of acute and chronic heart block, Br Heart J 27 916 1965

31. Haggerty R. V and Eley R C Varicella and cortisone Pediatrics 18 160 1956

32. Kilbourne, E. D and Hurstall, F L Lethal infection with Coxsackie virus of adult mice given cortisone Proc Soc. Exp Biol. Med. 77 135 1951

33. Ainger L. E. Mitral and aortic valve incompetence in endocardial fibroelastosis, Am J Cardiol 28 309 1971

34. Lower R. R. Cardiac transplantation *in* Norman J C editor Cardiac Surgery New York 19 2 Appleton Century Crofts, p 599

35. Simmons, R. L. Foker J E and Najarian J S Immunologic basis of cardiac allograft rejection in Norman, J C editor Cardiac Surgery New York 1972, Appleton-Century-Crofts, p 611

36. Apley J Primary myocardial disease in infancy clinical aspects, Arch. Dis Child. 36 366 1961

37. Miller R. A., and Hastreiter A R Myocarditis, The acute and chronic acquired primary myocardial disease of infants and children Am J Dis Child 100 36 1960

38. Williams, H., O Reilley R. H and Williams, A. Fourteen cases of idiopathic myocarditis in infants and children, Arch. Dis. Child. 28 271 1953.

39 Dye C L., Rosenbaum D Lowe J C Behnke R H. and Genovese P D Primary myocardial disease Part I Clinical feature Ann. Intern Med 58 426 1963

40 St. Geme J W Jr Noren G R Evans, C M., and Ozwoeld, L. On the nonautoimmune aspects of endocardial fibroelastosis with continued inquiry into the significance of delayed sensitivity to mumps virus Pediatrics 46 134 1970

41 Fixler D E Cole R B Paul, M H Lev M and Girod D A Familial occurrence of the contracted form of endocardial fibroelastosis, Am J Cardiol. 26 208 1970

42. Nielsen, J S Primary endocardial fibroelastosis in three siblings Acta Med. Scand. 177 145 1965

43 Klajman, A., Kamin Belsky N Feldman S and Kariv Z. Immunologic studies in familial cardiomyopathy Am. J Cardiol 28 707 1971

44 Black Schaffer B and Turner M E Hyperplastic infantile cardiomegaly Am J Pathol. 34 745 1958

45 Hastreiter A. R. and Miller R A Management of primary endomyocardial disease Pediatr Clin North Am 11 401 1964

46 Gersony W M Katz S L. and Nadas A S Endocardial fibroelastosis and the mumps virus Pediatrics 37 430 1966

47 Noren G R Adams, P and Anderson R C Positive skin reactivity to mumps virus in endocardial fibroelastosis, J Pediatr 62 604 1963.

48 Vosburgh, J B Diehl, A M Liu C., Lauer R M and Fabiyi, A Relationship of mumps to endocardial fibroelastosis. Complement fixation hemagglutination inhibition and intradermal skin tests for mumps in children with and without endocardial fibroelastosis Am J Dis. Child 109 69 1965

49 Sellers, F J Keith, J D and Manning J A The diagnosis of primary endocardial fibroelastosis, Circulation 29 49 1964

50 Harris, L. C and Nghiem Q X. Cardiomyopathies in infants and children Prog Cardiovasc Dis 15 255 1972

51 McLaughlin T G Schiebler G L. and Krovetz, L. J Endocardial fibroelastosis in American Negro children A distinct entity? Am Heart J 71 748 1966

52. Sommer A. Sanz, G., Craenen J and Newton W A Familial cardiomyopathy Birth Defects 8 1,8 1972

53 Phornphatkul, C Rosenthal, A and Nadas A S Cardiomyopathy in Noonan s syndrome Report of three cases, Br Heart J 35 99 1973

54. Bishop J M Campbell M and Jones E W Cardiomyopathy in four members of a family Br Heart J 24 715 1962

55 Hudson, R. E B Cardiovascular pathology Baltimore 1965 The Williams & Wilkins Company

56. Das, S K. Callen, J P Dodson V N., and Cassidy J T Immunologic binding in cardiomyopathic hearts, Circulation 44 612 1971

57 Gore I and Saphir O Myocarditis a classification of 1402 cases, Am Heart J 34 827 1947

58. Gore I Myocardial changes in fatal diphtheria A summary of observations in 221 cases Am J Med. Sci. 215 257 1948.

59 Montgomery J., Gear J., Prinslou F F., Kahn M and Kirsch, Z. B Myocarditis of the newborn. An outbreak in a maternity home in Southern Rhodesia associated with Coxsackie Group B virus infection S Afr Med J 29 608, 1955

60. Roberts, W C and Fox S A. III Mumps of the heart, Circulation 32 342, 1965

61 Moore C M., Henry J Benzing, G III and Kaplan S Varicella myocarditis, Am. J Dis. Child 118 899 1969

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REFERENCES

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7 Lambert E C and Vlad P Primary endomyocard[illegible] disease Pediatr Clin North Am 5 1057 1958.
8 Hamby R I and Raia F Electrocardiographic a[illegible] of primary myocardial disease in 60 patients Am Hea[illegible] J 76 316 1968
9 Goldman A M Acute myocarditis simulating myoca[illegible] dial infarction Dis. Chest 41 61 196?
10 Flowers N C and Horan L [illegible] Electrocardiograph[illegible] and vectorcardiographic features of myocardial disease *in* Fowler N D editor Myocardial diseases, New York 1973 Grune & Stratton Inc p 181
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13 McLaughlin T G Schiebler G L and Krovetz, L J Hemodynamic findings in children with endocardial fibroelastosis Am Heart J 75 162 1968
[illegible] Goodwin J F Cardiac function in primary myocardial disorders Part I Br Med J 1 1527 1964
15 Goodwin J F Cardiac function in primary myocardial disorders. Part II Br Med J 1 1595 1964

Pietras, R. J Meadows W R Fort M and Sharp J T Hemodynamic alterations in idiopathic myocardiopathy including cineangiography from the left heart chambers, Am. J Cardiol. 16 672 1965

Yu, N Schreiner B F Cohen J and Murphy W Idiopathic cardiomyopathy A study of left ventricular function and pulmonary circulation in 15 patients AM HEART J 71 330 1966

Hamby R. I Primary myocardial disease Medicine 49 55 1970

Dye, C. L., Genovese P D Daly W J and Behnke R. H. Primary myocardial disease Part II Hemodynamic alterations, Ann. Intern Med. 58 442 1963

Lynfield, J Gasul, B M Luan L. L and Dillon R F Right and left heart catheterizations and angiocardiographic findings in idiopathic cardiac hypertrophy with endocardial fibroelastosis Circulation 21 386 1960

Fowler N D Gueron M., and Rowlands D T Primary myocardial disease Circulation 23 498 1961

Graham, T P Jr Sarmakani, [redacted] W Canent [redacted] V Capp M. P and Spach M S Characterization of left heart volumes and mass in normal children and in infants with intrinsic myocardial disease Circulation 38 6 6 1968

Harvey W P Comments on symposium Circulation 32 857 1965

Burch, G E. Walsh J J Ferrans V J and Hibbs Q Prolonged bed rest in the treatment of the dilated heart Circulation 32 852 1965

Tilles, J [redacted] Elson S H Shaka J A Abelmann W Lerner A. M and Finland M Effects of exercise on coxsackie A9 myocarditis in mice Proc Soc Exp Biol. Med. 117 777 1964

Ainger L. E Somersill, B Fitch C W Lane N K and Harper W H. Corticosteroid therapy of acute nonrheumatic myocarditis, Am J Dis Child. 100 737 1960

Segal, J P Harvey W P and Gurel T Diagnosis and treatment of primary myocardial disease Circulation 32.837 1965

Mattingly J W The clinical concept of primary myocardial disease Circulation 32 845 1965

Ain er L. [redacted] Acute aseptic myocarditis corticosteroid therapy J Pediatr 64 716 1964

Aber L. P and Jones W W Corticotropin and corticosteroids in the management of acute and chronic heart block, Br Heart J 27 916 1965

Haggerty R. V and Eley R C Varicella and cortisone Pediatrics 18 160 1956

Kilbourne E D and Hurstall F L. Lethal infection with Coxsackie virus of adult mice given cortisone Proc Soc. Exp Biol. Med. 77 135 1951

Ainger L. E. Mitral and aortic valve incompetence in endocardial fibroelastosis, Am J Cardiol 28 309 1971

Lower R. R Cardiac transplantation in Norman J C editor Cardiac Surgery New York, 19 2 Appleton Century-Crofts, p 599

Simmons, R. L., Foker J F and Najarian J S Immunologic basis of cardiac allograft rejection in Norman, J C., editor Cardiac Surgery New York 19 2 Appleton-Century Crofts, p 611

Apley J Primary myocardial disease in infancy clinical aspects, Arch. Dis. Child 36 366 1961

Miller R. A and Hastreiter A. R. Myocarditis. The acute and chronic acquired primary myocardial disease of infants and children, Am. J Dis. Child 100 736 1960.

38 Williams, H O Reilley R. N and Williams A Fourteen cases of idiopathic myocarditis in infants and children, Arch. Dis. Child 28 71 1953

39 Dye C L. Rosenbaum D Lowe J C Behnke [redacted] H., and Genovese P D Primary myocardial disease Part I Clinical feature Ann Intern Med 58 426 1963

40 St Geme J W., Jr Noren G R Evans C M., and Ozwoeld, L. On the nonautoimmune aspects of endocardial fibroelastosis with continued inquiry into the significance of delayed sensitivity to mumps virus, Pediatrics 46 134 1970

41 Fixler D E Cole [redacted] B., Paul, M H., Lev M., and Girod, [redacted] A Familial occurrence of the contracted form of endocardial fibroelastosis, Am J Cardiol. 26 208 1970

42. Nielsen, J S Primary endocardial fibroelastosis in three siblings, Acta. Med. Scand. 177 145 1965

43 Klayman A., Kamin Belsky N Feldman S and Karev Z. Immunologic studies in familial cardiomyopathy Am. J Cardiol. 28 707 1971

44 Black Schaffer [redacted] and Turner M F Hyperplastic infantile cardiomegaly Am J Pathol 34 745 1958

45 Hastreiter A R and Miller R A Management of primary endomyocardial disease Pediatr Clin North Am. 11 401 1964

46 Gersony W M Katz S L. and Nadas, A. S Endocardial fibroelastosis and the mumps virus, Pediatrics 37 430 1966

47 Noren, G R Adams, P., and Anderson R C Positive skin reactivity to mumps virus in endocardial fibroelastosis, J Pediatr 62 604 1963

48 Vosburgh, J B Diehl, A. M Lin [redacted] Lauer R [redacted] and Fabiyi, A. Relationship of mumps to endocardial fibroelastosis. Complement fixation hemagglutination inhibition and intradermal skin tests for mumps in children with and without endocardial fibroelastosis Am J Dis Child 109 69 1965

49 Sellers, F J Keith, J D and Manning J A The diagnosis of primary endocardial fibroelastosis, Circulation 29 49 1964

50 Harris, L. C., and Nghiem, Q X. Cardiomyopathies in infants and children Prog Cardiovasc Dis 15 255 1972

51 McLaughlin T G Schiebler G L and Krovetz, L. J Endocardial fibroelastosis in American Negro children A distinct entity? AM HEART J 71 748 1966

52. Sommer A. Sanz, [redacted] Craenen J and Newton W A Familial cardiomyopathy Birth Defects 8 178 1972

53 Phornphatkul, C Rosenthal, A. and Nadas, A. S Cardiomyopathy in Noonan's syndrome Report of three cases, Br Heart J 35 99 1973

54 Bishop J M., Campbell, M., and Jones E W Cardiomyopathy in four members of a family Br Heart J 24 715 1962.

55 Hudson, R. E B Cardiovascular pathology Baltimore 1965 The Williams & Wilkins Company

56. Das, S K. Callen J P., Dodson V N and Cassidy J T Immunologic binding in cardiomyopathic hearts Circulation 44 612 1971

57 Gore I and Saphir O Myocarditis a classification of 1402 cases, AM. HEART J 34 827 1947

58 Gore L Myocardial changes in fatal diphtheria A summary of observations in 221 cases, Am J Med. Sci. 215 257 1948

59 Montgomery J Gear J., Prinslou, F F Kahn, M., and Kirsch, Z. G Myocarditis of the newborn An outbreak in a maternity home in Southern Rhodesia associated with Coxsackie Group B virus infection S Afr Med J 29 608 1955

60 Roberts, W C., and Fox S A. III Mumps of the heart Circulation 32 342, 1965

61 Moore C M., Henry J., Benzing, G., III and Kaplan S Varicella myocarditis, Am. J Dis Child. 118 899 1969

62 Bengtsson E Acute myocarditis and its consequences in Sweden Postgrad Med J 48 754 1972
63 Fine I Brainerd H and Sokolow M Myocarditis in acute infectious diseases Circulation 20 859 1959
64 Ross, L. J Electrocardiographic findings in measles Am J Dis Child 83 282 1952
65 Webster [illegible] [illegible] Cardiac complications of infectious mononucleosis. A review of the literature and report of five cases Am J Med Sci 234 62 1957
66 Fey L. D and Mills [illegible] A Fulminating trichonosis with myocarditis, Northwest Med. 53 701 1954
67 Jannach J R Myocarditis in infants with inclusions characteristic of psittacosis Am J Dis Child 95 734 1958
68 Hakkila J Frick H M and Halonen P I Pericarditis and myocarditis caused by toxoplasma Report of a case and review of the literature AM HEART J 65 758 1958
69 Wright H T Jr and Miller A Fatal infection in a newborn infant due to herpes simplex virus Report of a case diagnosed before death J Pediatr 67 130 1965
70 Obeyesekere I and Hermon Y Myocarditis and cardiomyopathy after arborvirus infections (dengue and Chiklungunya fever) Br Heart J 34 821 1972
71 Wilson R S E Morris T H and Rees J R Cytomegalovirus myocarditis Br Heart J 34 865 1972
72 Kibrick S Viral infections of the fetus and newborn Progr Med Virol 2 140 1961
73 Bolshakova A M Buiko V P Gromova L P and Raugald A A Peculiarities of the clinical picture and therapy of infectious allergic (nonspecific) myocarditis in children Indian Pediatr 5 107 1968
74 Ainger L. E Lawyer N G and Fitch C W Neonatal rubella myocarditis, Br Heart J 28 691 1966
75 Whitehead R Isolated myocarditis Br Heart J 27 220 1965
76 Rosenberg H S and McNamara D G Acute myocarditis in infancy and childhood Progr Cardiovasc Dis 7 179 1964
77 Saphir O and Cohen N A Myocarditis in infancy Arch. Pathol. 64 446 1957
78 Burch [illegible] E. Sun S C., Chu K C Sohal, R. S., and Colcolough H L. Interstitial and Coxsackie B myocarditis in infants and children J A M A 203 1, 1968
79 Pollen R. H Myocarditis due to Coxsackie virus, Group [illegible] Type 5 Am J Cardiol 12 736 1963
80 Vlad P., Rowe R D and Keith J D The electrocardiogram in primary endocardial fibroelastosis, Br Heart J 2 189 1955
81 Freundlich, [illegible] Munk, J Griffel, [illegible] and Steinlant, J Primary myocardial disease in infancy Am. J Cardiol, 13 721 1964
82 Manning J A., Sellers, F J., Bynam R. S and Keith, J D The medical management of clinical endocardial fibroelastosis Circulation 29 60 1964
83 Kariv I Kreisler B Sherf L. Feldman S and Rosenthal T Familial cardiomyopathy Am J Cardiol 28 693, 1971
84 Muehsam G E Pschibul F and Scerbo J E. The natural history of idiopathic cardiomegaly AM. HEART J 67 173 1964
85 Linde L. M and Adams, F H Prognosis in endocardial fibroelastosis, Am J Dis. Child 105 329 1963.
86 Konno S Sekiguchi, M., and Sakakibara S. Catheter biopsy of the heart, Radiol Clin North Am 9 491 1971
87 Shirey E K Hawk, W A Mukerji, [illegible] and Effler D B Percutaneous myocardial biopsy of the left ventricle Circulation 46 112 1972
88. Caves, P K Stinson E B Billingham M E., and Shumway N [illegible] Serial transvenous biopsy of the transplanted human heart Lancet 1 821 1974
89 Olsen [illegible] G J Diagnostic value of the endomyocardial bioptome, Lancet 1 658 1974
90 Sekiguchi, M and Konno [illegible] Diagnosis and classification of primary myocardial disease with the aid of endomyocardial biopsy Jap Circ J 35 737 1971

small-vessel disease in chronic

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a association between chronic alcoholism and ucal cardiac dysfunction has been confirmed numerous studies over the past decade [1-6] tmortem and biopsy investigations of the rt in chronic alcoholism have revealed basical similar gross light microscopic ultrastructur and cytochemical alterations [5-7] Less agree nt exists, however regarding the pathogenesis the myocardial changes It is as yet unclear iether alcohol is directly toxic to the heart[8-9] or ether it acts indirectly through its primary etabolic product acetaldehyde [10-11] Magnesium ficiency [1-2] altered catecholamine metabo m,[4-5] or other undefined mechanisms or bstances have been implicated by various inves gators. Additionally the proposal has been lvanced that the pathologic changes in chronic cohohc heart disease are not specific for alcohol xicity but may instead reflect the effects of ronic ischemia.[16-17]

Most pathologic studies of alcoholic heart sease have focused on the light and electron icroscopic alterations of the muscle fiber If the yocardial alterations in alcoholic cardiomyop thy are secondary to the effects of ischemia owever it is conceivable that these changes are ediated by disease of the small coronary vessels ecause large coronary vessel disease is usually bsent. Nevertheless little attention has been aid to the microvasculature of the myocar dium.

Several clinical and experimental studies have pointed to the existence of small vessel disease in chronic alcoholism Pintar and associates[3] in 1965 described significant changes in small intra myocardial vessels of three chronic alcoholics dying of cardiomyopathy The authors observed vascular edema and degeneration disorganiza tion of the vessel wall layers, and deposition of PAS-positive material in the subintima Sohal and Burch,[2] in an experimental study, fed mice a diet containing 15 per cent ethanol by volume for 3 months They noted ultrastructural changes in myocardial capillaries consisting of swollen and degenerating endothelial cells and narrowing of the vascular lumen The authors speculated on the role of chronic hypoxia induced by the vascular alterations in the pathogenesis of alco holic heart disease

Although as yet there is no conclusive evidence for the direct toxicity of alcohol on the heart the existence severity and extent of small vessel disease in the hearts of chronic alcoholics has been neither sufficiently examined nor critically evaluated Therefore the following study was instituted to determine the significance and degree of microvascular alterations in chronic alcoholism and to determine if any of the patho logic changes in alcoholic cardiomyopathy could be attributed to the vascular abnormalities

Materials and methods

The autopsy records of the Bronx Municipal Hospital Center were reviewed for the years 1972 and 1973 All patients under the age of 45 years dying secondary to alcoholic liver disease or chronic alcoholism were selected for further study A population of relatively young chronic alcoholics was chosen for analysis in order to minimize common cardiovascular complications of aging It was also considered likely that a young group would probably be heavier drinkers accounting for their early death from the effects of alcohol. Patients were eliminated if there was

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62 Bengtsson E Acute myocarditis and its consequences in Sweden Postgrad Med J 48 754 1972
63 Fine I Brainerd H and Sokolow M Myocarditis in acute infectious diseases Circulation 20 859 1959
64 Ross L J Electrocardiographic findings in measles Am J Dis Child 83 282 1952
65 Webster B H Cardiac complications of infectious mononucleosis A review of the literature and report of five cases Am J Med Sci 234 62 1957
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80 Vlad P Rowe R. D., and Keith J D The electrocardiogram in primary endocardial fibroelastosis, Br Heart J 2 189 1955
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83 Kariv I Kreisler B Sherf L Feldman S and Rosenthal T Familial cardiomyopathy Am J Cardiol 28 693 1971
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86. Konno S Sekiguchi M and Sakakibara S. Catheter biopsy of the heart Radiol Clin North Am 9 491, 1971
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any indication of hypertension, stenotic or occlusive coronary atherosclerosis (greater than 25 per cent of the vessel diameter), diabetes mellitus, hemochromatosis, congenital heart disease, history of rheumatic fever or evidence of rheumatic valvular lesions syphilis or systemic vasculitis of any type Nine patients were identified who fulfilled these criteria

The clinical histories of the nine patients were examined Special attention was paid to the type and duration of alcohol abuse, the use of medications or drugs which might affect the small vessels, evidence of malnutrition or chronic anemia and any symptomatology suggestive of cardiac failure Since all of these patients were admitted to the hospital with an acute surgical or medical problem relevant medications were noted which might acutely produce small vessel changes Finally, electrocardiographic radiographic, and laboratory data were examined to determine if any cardiovascular abnormalities were present

Control cases were selected from autopsies performed in 1972 1975 Nine cases were chosen comparable in age to the alcoholic study group The criteria for selection were identical to those of the study group in respect to the absence of any symptoms or pathologic evidence of cardiac disease None of the patients had a history of excessive alcohol intake Control cases were selected if there was a history of trauma (cutaneous burns) nonhypertensive or nonatherosclerotic central nervous system disease or documented nonalcoholic liver disease All control patients had acute symptomatology including sepsis, shock and hemorrhage similar to the alcoholic group The myocardial tissue was examined and evaluated in the same manner as the study group Microvascular abnormalities (see below) were tabulated for each case for the control group as a whole and for the three subgroups

The original histologic sections taken from the heart by several different prosectors were studied Wet tissue which was available in eight out of the nine study cases and seven out of nine control cases, was completely sectioned Tissue was routinely stained with hematoxylin and eosin and additional selected sections were stained with periodic acid–Schiff (PAS), Masson s trichrome, and elastic-van Gieson s stains Cardiac vessels were measured with a micrometer eyepiece The vessels were evaluated only if they were perpendicularly sectioned Vessels cut tangentially were counted as normal

The heart sections were scanned at low power, and the total number of intramyocardial epicardial vessels measuring approximately 50 to 200 microns were tabulated Vessels with obvious branching or double vessels within the same interstitial compartment were counted singly The total number of vessels per tissue section was established, and then the abnormal vessels within the section were studied at higher magnification The total number of abnormal vessels was tabulated, and a ratio was established between the abnormal and normal vessels for each tissue section and for the combined sections per case Ratios were established for the pathologic abnormalities noted below and then converted to percentages Since each vessel often had more than one pathologic alteration the same vessel could be scored more than once in several ratios

Vascular changes were tabulated in five categories, each of which included alterations of varying severity Questionable or truly minimal changes were scored as normal

1 *Vascular edema* This category included vessels demonstrating intracellular vacuolization, extracellular vacuoles and microcysts and loosening and disorganization of the vascular wall layers The presence of proteinaceous fluid or blood constituents such as leukocytes erythrocytes, or platelets within the vascular wall was also tabulated under this heading

2 *Vascular sclerosis* This group was composed of vessels with intimal and medial hyperplasia and/or fibrosis, elastic tissue proliferation and the deposition of PAS positive material in the vessel wall

3 *Perivascular fibrosis* This pertained to concentric perivascular hyaline fibrosis and also looser increased perivascular connective tissue, However, since it was difficult to determine where the adventitia ended and where fibrosis began it was decided to score as positive only those vessels surrounded by fibrous connective tissue which encroached upon and appeared to involve the adjacent myocardium

4 *Vascular inflammation* This included the presence within the vascular wall of obvious acute or chronic inflammatory cells or cells which have been assumed to be inflammatory

Table I Clinical features of the study group

Case No	Age/Sex	Duration of alcoholism (yr)	Type and amount of alcohol (per day)	Drug abuse	Therapeutic drugs
1	2?M	> 5	1 qt whiskey	None	Vasopressin
2	37F	NR†	NR	None	–
3	3 F	> 5	1 2 pints whiskey	None	–
4	41M	NR	1 pint whiskey	None	–
5	31M	> 2	1 qt gin or rum	Heroin methadone	Vasopressin
6	43M	22	5-6 pints beer	Heroin methadone	Vasopressin levarterenol
7	3?M	> 5	Wine (? amt)	None	Vasopressin
8	41M	NR	12 cans beer	None	Levarterenol
9	?1M	NR	1 qt whiskey	None	–

Mean age of group 36.1 years.
†NR, Not recorded.

Table II Pathological features and causes of death (study group)

Case No	Heart: Weight (Gm.)	Heart: Description	Liver	Other	Cause of death	Comments
1	400	Focal subendocardial hemorrhages	Cirrhosis fatty change	Varices gastric ulcers	GI hemorrhage	
2	3?0	Unremarkable	Cirrhosis fatty change	Pneumonia	Encephalopathy	
3	300	Unremarkable	Cirrhosis alc hepatitis	Septicemia	Hepatic failure	Macrocytic anemia
4	2?0	Fatty infiltration	Cirrhosis fatty change	Gastric ulcers GI hemorrhage	Hepatic failure	
5	30?	Unremarkable	Cirrhosis alc hepatitis	Varices pneumonia	GI hemorrhage	Heroin addict no vasculitis
6	4?0	Focal hemorrhage focal pericarditis	Cirrhosis	Varices	GI hemorrhage	Heroin addict no vasculitis
7	3?0	Unremarkable	Cirrhosis	Varices	GI hemorrhage	
8	520	Focal myocardial necrosis	Cirrhosis fatty change	Chronic pancreatitis	Unknown	Hemorrhagic diathesis after resuscitation
9	400	Unremarkable	Fatty change severe	Acute and chronic pancreatitis	Hemorrhagic pancreatitis	

i.e., Amitschkow myocytes Additionally perivascular accumulation of inflammatory cells which appeared to have a direct relationship to a vessel were scored within this category Diffuse perivascular and interstitial inflammation was noted separately

5. *Subendothelial humps* This referred to the presence beneath the endothelium of an asymmetric accumulation of smudgy eosinophilic material, usually acellular and variably compact which protruded into the vascular lumen If more than one subendothelial hump was present per vessel it was scored singly If there was a question regarding the presence of a hump vs the possibility of a tangential vessel section or the beginning of a branch point the vessel was scored as normal

Other parameters were noted but not formally tabulated These included the presence of interstitial fibrosis not directly related to vessels areas of myocardial fibrosis (healed microinfarcts) interstitial inflammation epicarditis recent or acute thrombosis of vessels and areas of acute myocardial infarction

any indication of hypertension, stenotic or occlusive coronary atherosclerosis (greater than 25 per cent of the vessel diameter), diabetes mellitus, hemochromatosis congenital heart disease, history of rheumatic fever or evidence of rheumatic valvular lesions syphilis, or systemic vasculitis of any type Nine patients were identified who fulfilled these criteria

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able IV Percentage of vascular abnormalities per case (study group)

Case No	Total vessels per case	Vascular edema (%)	Perivascular fibrosis (%)	Vascular sclerosis (%)	Subendothelial hump (%)	Vascular inflammation (%)
1	86	10	52	14	6	10
2	[illegible]	42	25	21	21	8
3	[illegible]	54	54	30	10	[illegible]
4	163	53	39	22	6	[illegible]
5	[illegible]	32	21	[illegible]	0	17
6	[illegible]	48	48	45	[illegible]	9
7	66	64	32	50	18	18
[illegible]	111	[illegible]	59	[illegible]	10	16
9	190	57	[illegible]	47	15	16
Totals	[illegible]	48	42	36	13	11

Computed as follows: % = $\frac{\text{total abnormal vessels per group}}{\text{total vessels examined}} \times 100$

Table V Percentage of vascular abnormalities (control group)

Case No	Total vessels per case	Vascular edema (%)	Perivascular fibrosis (%)	Vascular sclerosis (%)	Subendothelial hump (%)	Vascular inflammation (%)
Trauma group						
10	181	[illegible]	10	28	08	0
11	117	23	10	16	03	01
12	107	16	11	18	01	01
Totals	[illegible]	27	10	21	05	01
CNS group						
13	63	27	05	10	[illegible]	02
14	0	[illegible]	06	0	01	0
15	125	[illegible]	06	11	01	02
Totals	258	25	06	08	01	02
Hepatic group						
6	112	38	41	14	0	[illegible]
17	92	15	18	2	07	[illegible]
18	84	17	[illegible]	06	[illegible]	[illegible]
Totals	287	[illegible]	24	14	09	04
Totals for group	950	26	13	15	03	02

and 8 exceeded 400 grams None of the hearts was described as flabby and none had overt coronary atherosclerosis or mural thrombi Several hearts had focal, probably terminal subendocardial hemorrhages and No 8 had focal myocardial necrosis. With the exception of case 8 the hearts were generally described as unremarkable

Microscopically however careful examination of the small vessels of the myocardium revealed significant alterations The total number of vessels studied per case and the percentage of abnormal vessels for the alcoholic group is summarized in Table IV and for the control group in Table V

The most frequent alteration noted was vascular edema which was present in 48 per cent of the vessels from all nine alcoholic cases (Table IV) This compares with an incidence of 26 per cent in the control group The changes consisted of both intracellular and extracellular edema Empty looking vacuoles were frequently noted within the cells of the intima and media This was possibly of little consequence and may have been the result of terminal *antemortem* changes or

Table III Pathological features and causes of death (control cases)

Case no	*Age/Sex**	*Primary diagnosis*	*Other*	*Causes of death*	*Comment*
10	40F	40% 3 flame burns	Acute pneumonia respiratory insufficiency	Sepsis	
11	38M	40% 2 and 3 flame burns	Necrotizing laryngobronchitis stress ulcers hemolytic anemia	Shock	
12	40F	40% 2° and 3° flame burns	Bronchopneumonia wound infection	Sepsis	Drug addict
13	37F	Malignant glioma of thalamus	Cerebral edema meningitis bronchopneumonia	Cerebral edema	Multiple operative procedures (4 mo. course)
14	37M	Parietal arteriovenous malformation	Subarachnoid hemorrhage bronchopneumonia	Subarachnoid hemorrhage	
15	43F	Middle cerebral artery embolus with encephalomalacia	Massive pulmonary emboli	Acute pulmonary emboli	
16	22M	Post hepatitic cirrhosis	Acute gastric ulcer esophageal varices	Massive GI hemorrhage	Post transfusion hepatitis congenital abnormalities ? congenital toxoplasmosis
17	26M	Wilson s disease	Cirrhosis esophageal varices	Massive GI hemorrhage	
18	30F	Acute viral hepatitis	Diffuse gastric hemorrhage	Acute viral hepatitis (hepatic failure)	

Mean age of group 34 7

Results

There were seven men and two women in the study group (see Table I) The mean age was 36 1 years (range 27 to 43 years) All nine patients were known chronic alcoholics who had been drinking heavily for at least several years prior to their terminal admissions In cases 6 and 9 the patients admitted to alcohol abuse for 22 years There were four whiskey drinkers, two beer drinkers and one drinker each of wine and gin In case 2 the type of alcoholic beverage was not recorded All nine patients were generally described as well nourished although patient 9 had lost 35 pounds in the year preceding admission The five patients who presented with acute upper gastrointestinal hemorrhage could not be evaluated for chronic anemia Only patient 3 among the four remaining nonbleeding patients, was noted to have a macrocytic and hypochromic anemia with a hematocrit of 24 volumes per cent Two patients Nos 5 and 6 had been heroin addicts in the past and were allegedly on methadone maintenance Neither patient had a history of chronic viral hepatitis or of vascular complications of drug abuse None of the patients had a history of cardiac symptoms, although several had episodic shortness of breath and dyspnea relieved by paracentesis There was no indication of cardiomegaly noted on physical examination or chest x ray The electrocardiogram was unremarkable in all patients in whom it was recorded

The major pathologic findings and cause of death are summarized in Tables II and III Within the alcoholic group three patients died of hepatic failure four died of massive variceal hemorrhage and one died of acute hemorrhagic pancreatitis Patient 8 had a sudden cardiopulmonary arrest of unknown etiology outside of the hospital was resuscitated, but died 2 days after admission secondary to complications of anoxia Eight of the nine patients had micronodular cirrhosis, whereas patient 9 had severe hepatic fatty change without cirrhosis Within the control group two patients died of sepsis, two died of massive upper gastrointestinal hemorrhage and one each died as the result of burn shock subarachnoid hemorrhage, cerebral edema acute pulmonary emboli and acute hepatic failure

The alcoholic hearts, with two exceptions were not remarkably enlarged The mean cardiac weight was 370 grams Only the hearts in cases 6

Table IV Percentage of vascular abnormalities per case (study group)

Case No	Total vessels per case	Vascular edema (%)	Perivascular fibrosis (%)	Vascular sclerosis (%)	Subendothelial hump (%)	Vascular inflammation (%)
1	86	10	52	14	6	10
2	125	42	25	21	21	8
3	.0	54	54	30	10	10
4	163	53	39	22	6	2
5	"5	32	21	35	0	17
6	128	48	48	45	27	9
7	66	64	32	50	10	18
8	111	56	[illegible]	50	10	16
9	190	57	45	47	15	16
Totals	994	48	42	36	13	11

Computed as follows $\% = \frac{\text{total abnormal vessels per group}}{\text{total vessels examined}} \times 100$

Table V Percentage of vascular abnormalities (control group)

Case No	Total vessels per case	Vascular edema (%)	Perivascular fibrosis (%)	Vascular sclerosis (%)	Subendothelial hump (%)	Vascular inflammation (%)
Trauma group						
10	181	37	10	26	08	0
11	117	23	10	16	03	01
[illegible]	107	16	11	18	01	01
Totals	405	27	10	21	05	01
CNS group						
13	63	27	05	10	02	02
14	0	23	06	0	01	0
15	1.5	24	06	11	01	02
Totals	258	"5	06	08	01	0?
Hepatic group						
16	111	36	41	14	0	05
17	92	15	18	22	07	05
18	84	17	07	06	06	0
Totals	287	24	24	14	09	04
Totals for group	950	26	13	15	03	02

and 8 exceeded 400 grams None of the hearts was described as flabby and none had overt coronary atherosclerosis or mural thrombi Several hearts had focal probably terminal subendocardial hemorrhages and No [illegible] had focal myocardial necrosis With the exception of case 8 the hearts were generally described as unremarkable

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Fig 1 There is extensive vascular disorganization with large clear spaces and focal sclerosis producing disruption and separation of the vessel wall layers (Trichrome ×100)

Fig 2 The vessel lumen is on the upper right There are several subendothelial cystic spaces in which obvious red blood cells can be seen There is a gap (arrow) between the endothelial cells through which the erythrocytes appear to pass (Hematoxylin and eosin ×1 000)

postmortem autolysis More significant was the presence of edema, which appeared to be extracellular There was separation of individual cells within the vessel wall by clear spaces, which often extended into the media When these changes were more pronounced and confluent, there was marked separation and disorganization of the vessel wall layers (Fig 1) Occasionally subendothelial microcysts were present filled with eo[sino]philic material Infrequently these microcys[ts] were noted to contain erythrocytes or leukocyte[s] (Figs 2 and 3) Irregular cystic spaces were al[so] noted in the media of several larger vessels (50 t[o] 200 microns) which contained basophilic materia[l] most likely representing intercellular groun[d] substance

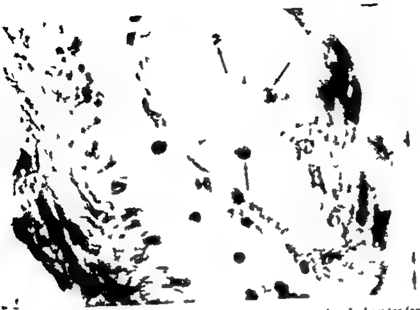

Fig 3 A large subendothelial microcyst on the right contains several mononuclear leukocytes (arrows) and red blood cell fragments (arrowheads) The fibrillar material within the cyst is stained eosinophilic (Trichrome ×400)

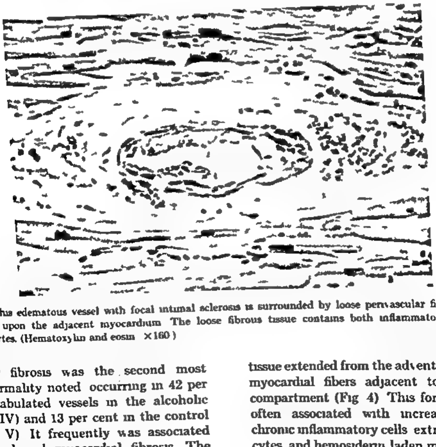

Fig 4 This edematous vessel with focal intimal sclerosis is surrounded by loose perivascular fibrosis which impinges upon the adjacent myocardium The loose fibrous tissue contains both inflammatory cells and erythrocytes. (Hematoxylin and eosin ×160)

Perivascular fibrosis was the second most common abnormality noted occurring in 42 per cent of the tabulated vessels in the alcoholic group (Table IV) and 13 per cent in the control group (Table V) It frequently was associated with interstitial and myocardial fibrosis The perivascular fibrosis was predominantly of two types. Loose poorly organized fibrous connective tissue extended from the adventitia to involve the myocardial fibers adjacent to the interstitial compartment (Fig 4) This form of fibrosis was often associated with increased numbers of chronic inflammatory cells extravasated erythrocytes and hemosiderin laden macrophages in the perivascular interstitium No active vasculitis was noted Denser more organized perivascular

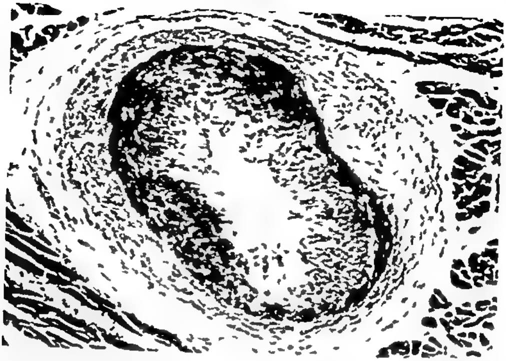

Fig 5 Dense concentric perivascular fibrosis surrounds this vessel with striking intimal proliferation and edema and medial sclerosis (Trichrome ×63)

Fig 6 There is circumferential vascular sclerosis and relatively dense perivascular fibrosis, producing narrowing of the lumen The vessel wall is focally infiltrated by Anitschkow myocytes which cannot be resolved at this magnification (Hematoxylin and eosin ×160)

fibrosis consisted of concentric, hyalinized variably acellular fibrous tissue (Fig 5) This form of fibrosis was usually not associated with increased interstitial inflammation It was commonly seen within papillary muscles, but was also scattered throughout the myocardial sections examined Although not tabulated separately from the looser less organized fibrosis, the concentric fibrosis generally was the less common of the two forms

Vascular sclerosis was noted in 36 per cent of the vessels examined in the alcoholic group (Table IV), compared to 15 per cent of the vessels in the control group (Table V) Several types of abnormality were apparent Subendothelial intimal thickening was noted, similar in composition and staining characteristics to the subendothelial humps described below The major difference however was that the sclerosis was not nodular but was a linear intimal thickening occurring

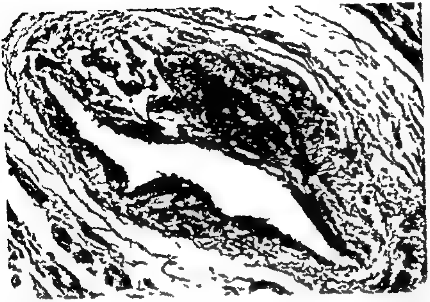

Fig 7 There is asymmetric vascular sclerosis and focal vascular wall edema with extensive disruption and duplication of black staining elastic tissue (Elastic van Gieson ×100)

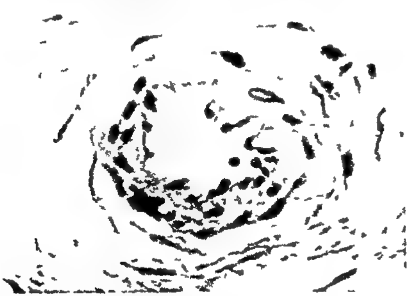

Fig 8 Two small subendothelial humps are present in this otherwise relatively normal vessel. The surface covering of endothelial cells can be appreciated Serial sections revealed that these humps did not represent a vascular branch point (Hematoxylin and eosin ×400)

along one portion of a vessel wall. Asymmetric medial sclerosis was also noted in which intimal and medial fibrosis occurred along a short segment of the vessel wall. This type of sclerosis usually did not markedly encroach upon the vascular lumen Major encroachment and narrowing of the lumen often was present when the sclerosis affected the entire vessel wall in a symmetrical fashion (Fig 6) Trichrome stains revealed increased connective tissue within sclerotic vessel walls and stains for elastica revealed reduplication and fragmentation of elastic fibers (Fig 7)

Subendothelial humps were present in 13 per cent of all vessels tabulated in the alcoholic group (Table IV) and in 3 per cent of the vessels in the control group (Table V) The humps consisted of subendothelial accumulations of brightly eosinophilic PAS-positive material with a granular and occasionally hyalinized appearance (Fig 8) The

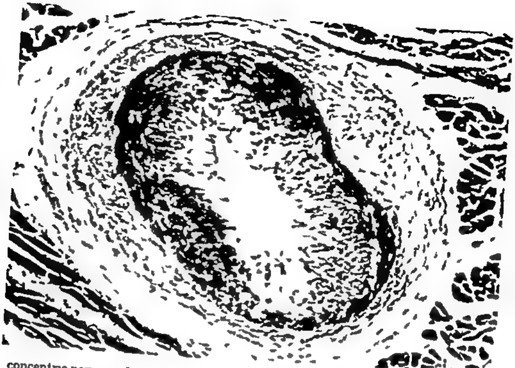

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Fig 11 A sclerotic vessel on the left is lying within an area of myocardium which reveals extensive replacement by fibroblasts chronic inflammatory cells and capillaries (case 9) (Hematoxylin and eosin ×63)

V) and in 2 per cent of the vessels in the control group (Table V) None of these 18 cases had gross or microscopic evidence of rheumatic heart disease nor did there appear to be increased numbers of Anitschkow cells in the interstitium Yet unequivocal Anitschkow myocytes with a typical caterpillar like chromatin pattern when viewed in longitudinal section or an owl s eye appearance when seen in cross section were noted (Figs. 9 and 10) No fibrinoid necrosis or heavy inflammatory infiltrate was identified in association with these cells They could easily be separated histologically from both endothelial cells and the elongated smooth muscle cells composing the vascular wall. It was not possible to determine if the Anitschkow cell originated from the adventia periadventitial connective tissue or the vascular lumen Mononuclear cells with indented nuclei and a rim of cytoplasm resembling circulating monocytes were rarely noted sticking to the endothelium The significance of these circulating cells in relation to the presence of Anitschkow myocytes within the vessel wall could not be determined

Despite the lack of cardiac symptoms in the nine alcoholic cases and despite the absence of gross cardiac abnormalities suggesting a diagnosis of alcoholic cardiomyopathy all nine cases demonstrated varying degrees of myocardial alteration Myofiber atrophy and variability in size associated with edema fibrosis and chronic inflammation of the interstitium were noted focally in cases 1 2 4 [illegible] 8 and 9 The most severe changes were present in case 9 in which there was extensive interstitial fibrosis chronic inflammation and active fibroblastic proliferation (Fig 11) Focal acute myocardial necrosis was noted in cases 2 and 8 but this was attributed to terminal tissue hypoxia Focal areas of myocardial ischemia were only rarely noted in the control group

It should be pointed out that the methods utilized in this study have produced a quantitative index of vascular abnormalities in both the alcoholic and control groups Since qualitative abnormalities were not tabulated it is difficult to compare the raw figures from one group to the other As a subjective observation however the vascular abnormalities in the control group with one exception did not approach the severity of the changes described in the alcoholic group Endothelial disruption large subendothelial spaces with loosening of the vessel wall layers marked vascular sclerosis and onion skin-like perivascular fibrosis were not commonly noted in the control group The one exception was case 16 in which changes particularly perivascular fibrosis comparable to the alcoholic patients were seen This patient had a posthepatitic cirrhosis with multiple congenital abnormalities and questionable congenital toxoplasmosis It is unclear whether these diseases contributed to the cardiac

Fig 9 Several typical Anitschkow myocytes are present within the intima and media of this vessel Two cells with a central longitudinal mass of chromatin can be seen to the right of center (arrows) (Hematoxylin and eosin ×400)

Fig 10 A characteristic caterpillar like chromatin pattern can be seen in this Anitschkow myocyte which is lying within the intima The vessel lumen is on the upper left (Hematoxylin and eosin ×1 000)

humps were generally acellular although mono nuclear cells and cell fragments were infrequently noted within the eosinophilic material The humps protruded into the vascular lumens and ranged in size from 10 to 25 microns Only the larger humps occurring in the smaller vessels appeared to significantly narrow the vascular lumen In the rare vessels which had more than one hump however there appeared to be marked narrowing and distortion of the vascular chan nel

The most unusual and unexpected finding in this study was the observation of Anitschkow myocytes and rarely other inflammatory cells within the intima and media of 11 per cent of the vessels examined in the alcoholic group (Table

edema was felt to be the consequence of increased vascular permeability resulting in the passage of protein rich plasma through the endothelium where it accumulated between the vascular wall layers. Organization of this fluid would then result in gradual occlusion of small vessels with subsequent anoxic effects on small areas of myocardium. Observation of vascular wall edema was noted by Benchimol and Schlesinger in their study of beriberi heart disease. In the present report vascular wall edema was the most common abnormality seen, occurring in 48 per cent of the vessels examined.

Several experimental studies relevant to vascular pathology in alcoholism have been reported. Constantinides has found that many agents produce either necrosis of arterial endothelium or widening of intercellular gaps allowing the passage of circulating macromolecules into the vascular wall where they accumulate. Among the agents which he studied, serotonin and the catecholamines induced enlarged endothelial cell junctions and intracellular and extracellular fluid concentration. In circumstances other than alcoholism, such as pheochromocytoma or iatrogenic administration, excessive catecholamines are known to produce myocardial injury of unknown etiology with vascular damage being one of the postulated mechanisms. Of interest in this regard is the work of James and Bear who have observed that acetaldehyde, the principal first metabolic product of ingested alcohol, releases myocardial and adrenal stores of norepinephrine as well as serotonin. It is as yet unclear whether these released amines play a role in the induction of the vascular changes in alcoholic heart disease.

Experimentally, the effect of ethanol administration on the myocardial capillaries of mice has been studied by Sohal and Burch. They noted swelling and degeneration of endothelial cells and the passage of erythrocytes through junctional gaps in the endothelial lining. Eventually narrowing and irregularity of the vascular lumen resulted. The authors considered the possibility that chronic hypoxia due to the vascular alterations might play a role in the production of alcoholic myocardial disease. They also speculated that the pathologic changes were the result of the altered metabolism of serotonin and other biogenic amines secondary to the administered ethanol.

Magnesium deficiency has been incriminated as a contributing factor in alcoholic cardiomyopathy. Its effects on the heart have been studied by Wener and associates. They noted that chronic magnesium deficiency in dogs induced focal intimal disruption in small myocardial vessels as well as edema and degeneration of the media. Adventitial edema was also occasionally present. In medium sized myocardial vessels loose arrangement of the vessel wall with a suggestion of edema was noted. The vascular changes described in their paper were remarkably similar to many of the abnormalities noted in the present study. It is known that magnesium deficiency commonly occurs in chronic alcoholism. Lim and Jacob found diminished skeletal muscle magnesium levels in nine of 10 chronic alcoholics studied.

It is conceivable that many or all of these mechanisms may have played a role in the pathogenesis of the vascular edema observed in the present study. The experimental data suggesting that the edema is secondary to endothelial cell damage, widening of intercellular gaps, and diffusion of plasma into the vascular wall are supported by the observation of erythrocytes and leukocytes within intimal spaces (Figs. 2 and 3). Very little is known about the fate of edema fluid macromolecules or even cells which have permeated into the intima. It is unclear how these substances are specifically handled by vascular wall myocytes and inflammatory cells and how the presence of edema fluid elicits the various forms of microvascular pathology described in this report. Future study will be required to define the precise mechanisms involved; however, a possible sequence can be proposed.

Localized vascular wall injury leading to focal subendothelial accumulation of plasma protein and macromolecules may induce vascular wall myocytes to deposit PAS positive basement membrane-like material, elastin, and collagen. The end result would be a subendothelial hump. This sequence has been proposed by Haerem in a study of identical lesions in 215 consecutive autopsies. More extensive endothelial injury could result in either partial or circumferential vascular sclerosis. Vascular sclerosis of varying severity was a relatively common finding in this study, occurring in 36 per cent of the examined vessels. The presence of increased connective tissue and reduplicated elastic fibers in these lesions may thus be secondary to a diffuse induc

microvasculature abnormalities Even with this case included in the control group, however, the tabulated subtotals for the hepatic patients (cases 16 to 18) did not differ appreciably from those of the trauma and central nervous system patients or from those of the control group as a whole

The differences between the alcoholic and control groups were not statistically analyzed because of the small sample population However, comparison of the data in Tables IV and V reveals a two to threefold increase in the incidence of major vascular abnormalities (vascular edema, perivascular fibrosis and vascular sclerosis) when the alcoholic group is compared to the control group The less significant abnormalities, subendothelial humps and vascular inflammation were approximately five times more common in the alcoholic group Admittedly within the small sample population studied, there was a degree of overlap which makes absolute diagnosis of alcoholic heart disease on the basis of vascular pathologic changes difficult however the over all trend suggests a definitively increased incidence of damaged vessels in the alcoholic heart

Discussion

Alcoholic heart disease has been estimated to account for up to 3 per cent of cardiac patients in large municipal and veterans hospitals[20] A syndrome consisting predominantly of cardiomegaly tachycardia, and cardiac failure is associated with chronic alcoholism[1] probably occurring independently of vitamin deficiency[1] malnutrition[6] and known cardiotoxic substances present in alcohol such as cobalt[6,8] A preclinical form of heart disease in chronic alcoholics manifested by decreased cardiac output and elevated left ventricular end diastolic pressures has been described in alcoholics without radiographic evidence of cardiomegaly or symptoms of heart failure[8,20] A similar group of patients comprised the present study

It has been exceedingly difficult to define the etiologic agent or agents involved in the pathogenesis of alcoholic heart disease Most studies by necessity have dealt with chronically ill adult patients who have varying nutritional intake uncontrolled vitamin and electrolyte levels increased susceptibility to infections, as well as the normal afflictions associated with aging In addition, the amount and type of alcohol ingested is often an unknown variable Anima ... have produced contradictory results Whereas Burch and associates[1] using the mouse have reported evidence supporting the concept of direct alcohol toxicity on the heart, their results have been disputed by Hall and Rowlands,[1] who were not able to induce toxic changes In human subjects, Regan[*] has documented the effects on myocardial function of large doses of alcohol administered acutely and chronically Others, however, doubt the direct etiologic connection between alcohol and heart disease

Less debatable is the relative constancy of the pathologic changes reported by various observers Despite the occasional severity of clinical alcoholic heart disease, the pathologic alterations described by light microscopy are relatively minimal and consist of variable fibrosis lipid deposition and interstitial edema[1,5,7] Ultrastructurally dilatation of the sarcoplasmic reticulum and mitochondrial degeneration have been reported by Alexander[1] Cytochemical study has revealed varying degrees of myocardial enzyme depletion[4] These alterations are strikingly nonspecific and may only reflect electrolyte imbalance or tissue anoxia[16,17] As noted in the introduction almost all pathologic studies of alcoholic heart disease have focused on myofiber alterations with little attention paid to the intramyocardial vessels However if tissue anoxia plays a major role in the pathogenesis of alcoholic cardiomyopathy abnormal intramyocardial small coronary arteries may be the mediators of this anoxia since the epicardial coronary arteries are usually normal

The report by Pintar and associates[1] in 1965 has been cited in numerous papers as evidence for the existence of small vessel disease in alcoholic heart disease Yet the vascular abnormalities were only briefly described in the course of reporting three cases of alcoholic cardiomyopathy without comments on the frequency of the changes Since 1965 to the best of our knowledge there have been no reported systematic studies of the cardiac microvasculature in chronic alcoholism The present study has attempted to define the types and frequency of vascular alterations in the hearts of chronic alcoholics without overt cardiomyopathy

Pintar and associates[18] considered vascular wall edema to be the primary abnormality of the microvasculature in chronic alcoholism This

ficiency It is probable however that there are multiple etiologic factors which affect the small cardiac vessels of the chronic alcoholic

Finally the proposal was advanced that the nonspecific pathology of the myocardium in chronic alcoholism may be a result of ischemia secondary to disease of the small intramyocardial coronary arteries

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REFERENCES

1. Alexander C S Idiopathic heart disease Analysis of 100 cases, with special reference to chronic alcoholism Am J Med 41 1?13 1966
 Koide T., Machida, K. Nakanishi, A Ozeki K Mashima S and Kono, H Cardiac abnormalities in chronic alcoholism Jap Heart J 13 418 19?2.
 Evans, W Alcoholic myocardiopathy Prog Cardiovasc Dis. 7 151 1964
 Demakis J G Proskely A Rahimtoola S H Jamil, M Sutton, G C Rosen K. M., Gunnar R M and Tobin, J R Jr The natural course of alcoholic cardiomyopathy Ann. Intern Med. 80 293 1974
 Brigden W Alcoholic cardiomyopathy Cardiovasc Clin. 4 197 19 2.
 Burch G E and DePasquale N P Alcoholic cardiomyopathy Am. J Cardiol. 23 723 1969
 Morales, A R Cardiomyopathies Congenital and acquired, in Edwards, J E editor The heart, Baltimore 19?4 The Williams & Wilkins Company pp 221 225
 Regan T J Ethyl alcohol and the heart Circulation 44 9?7 1971
 Gould L Cardiac effects of alcohol Am Heart J ?? 422 19 0
 James, T N and Bear E S Effects of ethanol and acetaldehyde on the heart Am Heart J 74 243 1967
 Mitchell, J H and Cohen L S Alcohol and the heart Mod. Concepts Cardiovasc Dis 39 (Suppl) 109 19?0
 Wiener J Pintar K Simon M A Motola R Friedman, R., Mayman A and Schucher R The effects of prolonged hypomagnesemia on the cardiovascular system in young dogs, Am Heart J 67 221 1964
13. Fankushen D Raskin, D., Dimich, A., and Wallach S E. The significance of hypomagnesemia in alcoholic patients, Am. J Med 37.802 1964
14. Anton A H Ethanol and urinary catecholamines in man Clin. Pharmacol. Ther 6 462, 1965
15. Sohal, R S and Burch, G E Effect of ethanol ingestion on the myocardial capillaries of mice Cardiovasc Res. 3 369 1969
16. Morin Y., and Cote G Toxic agents and cardiomyopathies, Cardiovasc. Clin 4 251 1972.
17. Burch, G E., Colcolough, H L., Harb J M., and Tsui, C Y The effect of ingestion of ethyl alcohol wine and beer on the myocardium of mice Am J Cardiol. 27 522 1971
18. Pintar K., Wolanskyj B M., and Buggay E. R Alcoholic cardiomyopathy Can Med Assoc J 93 103 1965
19. Robbins, S L. Cardiac pathology—A look at the last five years, Hum. Pathol. 5 9 1974
20. Asokan S K., Frank M J and Witham A C Cardiomyopathy without cardiomegaly in alcoholics, Am Heart J ?? 13 1972.
21. Hall, J L., and Rowlands, D T Jr Cardiotoxicity of alcohol, Am. J Pathol. 60 153 19?0
22. Goodwin, J F., and Oakley C M The cardiomyopathies, Br Heart J 34 545 1972.
23. Alexander C S Electron microscopic observation in alcoholic heart disease Br Heart J 29 200 1967
24. Ferrans, V Hibbs, R., Weilbaecher D., Black W., Walsh, J and Burch, G Alcoholic cardiomyopathy A histochemical study Am Heart J 69 748 1965
25. Benchimol A B and Schlesinger P Beriberi heart disease. Am. Heart J 46 245 1953
26. Constantinides, P The important role of endothelial changes in atherogenesis, in Shimamoto T., Numano F., and Addison G M editors Atherogenesis, Amsterdam 1972, Excerpta Medica Foundation pp 51-65
27. Haft J I Cardiovascular injury induced by sympathetic catecholamines Prog Cardiovasc Dis. 17 ?3 19?4
28. Lim P and Jacob E., Magnesium status of alcoholic patients, Metabolism 21 1045 1972
29. Haerem, J W Cusion like intimal lesions and platelet aggregates in intramyocardial arteries of man Acta Pathol Microbiol. Scand 77 73 1969
30. Hall E M and Anderson L R The incidence of rheumatic stigmas in hearts which are usually considered non rheumatic Am Heart J 25 64 1943
31. Nakano J Cardiovascular actions of vasopressin Jap Circ J 37 363 19?3

tion of vascular wall myocytes by edema fluid to produce these substances. Finally, perivascular fibrosis may be the result of organization of edema fluid which has diffused through the entire vascular wall into the interstitial space. Similar fibrosis was present around edematous medium sized vessels of the hypomagnesemic dogs described by Wiener and associates.[1] The frequency of the abnormality in this study (42 per cent) suggests that it occurs with great regularity in chronic alcoholics.

Further evidence of a primary toxic vascular injury in chronic alcoholism is suggested by the observation of vascular wall inflammation in 11 per cent of the vessels in this study. The inflammation consisted predominantly of individual or occasionally aggregated typical Anitschkow myocytes within the intima or media. Anitschkow myocytes have been noted as a component of the vessel wall in rheumatic vasculitis,[11] but to the best of our knowledge they have never been described in nonrheumatic cardiac disease. None of the nine patients of this study had any clinical or pathologic evidence of antecedent rheumatic heart disease. Anitschkow myocytes were rarely noted in the control group within vessel walls which were otherwise tabulated as abnormal. Additionally, they have occasionally been seen within intramyocardial vessel walls in patients with sickle cell anemia, congestive cardiomyopathy, and ischemic and hypertensive heart disease (personal observations, unpublished). Therefore, if in fact Anitschkow myocytes represent a histiocytic cell, we must assume that their presence in the vascular wall is a reaction to vascular injury of unknown etiology. Additionally, they may play an important role in the organization of the material which permeates into the vessel.

Despite the clinical absence of cardiac symptomatology in this group of nine patients, the severity and frequency of the vascular abnormalities was reflected in the extent of the myocardial pathology. Interstitial and myocardial degenerative changes were noted with varying degrees of severity in the entire group. Although it is possible that the acute administration of vasopressin and levarterenol to several of the patients in this group (see Table I) may have induced vascular and myocardial alterations,[27-31] it is unlikely that any of the more chronic changes described were caused by these agents.

It is probable that the etiology of small vessel disease in chronic alcoholism is multicausal. The cardiac microvasculature appears to have a limited response to varying toxic agents, whether they be catecholamines, serotonin, cobalt or alcohol, as well as to varying deficiencies such as thiamine or magnesium. The end result is the induction of endothelial damage, vascular edema and subsequent vascular and perivascular sclerosis. The nonspecific myocardial alterations reported in chronic alcoholism may then be the consequence of the vascular disease. The results of this study suggest that more attention should be paid to the microvasculature in alcoholic cardiomyopathy, and possibly in other nonatherosclerotic myocardial diseases.

Summary

A morphologic study of the small (50 to 200 micron) intramyocardial coronary arteries was performed. The cases chosen for study were selected from a relatively young group of patients without clinical evidence of alcoholic cardiomyopathy or pathologic evidence of large coronary artery disease in order to evaluate alterations in the small vessels which could possibly be attributed to the chronic alcoholic state.

Five basic vascular abnormalities were described. The most common alteration found in all nine cases was vascular wall edema (48 per cent) followed by perivascular fibrosis (42 per cent), vascular sclerosis (36 per cent), subendothelial humps (13 per cent), and vascular wall inflammation (11 per cent). The significance and pathogenesis of these changes were discussed. Primary endothelial cell damage was proposed as a common pathogenic mechanism for all five types of vascular abnormality. It was suggested that following endothelial damage, fluid and macromolecules penetrate into the vessel wall or into the perivascular space where by incompletely understood processes they induce vascular wall myocytes to produce collagen, elastin and basement membrane-like substances. Evidence supporting this mechanism was derived from the common observation of vascular wall edema, from the occasional presence of erythrocytes and leukocytes within the vessel wall, and from experimental data in the literature.

Several possible etiologic agents were implicated in the pathogenesis of endothelial and vessel wall injury. These included alcohol itself, acetaldehyde, biogenic amines, and magnesium

brachial artery Pressure transducers were adjusted to the level of the fourth interspace anteriorly while the individuals were sitting or walking. Mean arterial pressures were obtained by electrical integration Oxygen contents were measured with a Lex O_2 Con analyzer[a] $\dot{V}O_2$ was measured by the open circuit method [a] Polarcardiographic coordinates for spatial magnitudes and vector angles of the P R ST and T forces of the Frank x, y and z leads were measured to quantify the magnitude of the ischemic responses The recently described new criterion, MS [11] and changes in S-T slopes [2] were also computed

Observations were made at rest in the supine and sitting postures, and during exercise performed to the limits of fatigue

Data were organized in relation to the final minute of maximal exercise for each subject to describe the hemodynamic approach to this limit, as reported in men [13]

Results

The four women with upsloping ST segment depression of 1 mm or more at maximal exercise were coincidentally older (56 vs. 51 years) than the six in the ST negative group heavier (relative weights* of 109 per cent vs 102 per cent) and had higher resting systolic pressures. In 1973 when maximal oxygen uptake was also measured the four ST positive women also had higher resting systolic pressures (126 ± 9 mm Hg vs 114 ± 11 mm. Hg) K levels at rest were similar in both groups.

Maximal oxygen uptakes ($\dot{V}O_{2m}$) in the two groups were virtually identical (Table II) Weight adjusted $\dot{V}O_{2m}$ was insignificantly higher in the ST negative group than in the ST positive group [26 1 ± 1 8 ml /(kg min) vs 24 0 ± 5 3 ml /(kg min)] Maximal ventilatory volume (V_E) was 45 9 ± 13 8 L per minute in the ST negative group and 46 5 ± 8 1 L per minute in the ST positive group

The relationship between cardiac output and oxygen uptake during exercise showed a high correlation ($r = +0\ 92$) with a SEE of 0 59 L per minute (Fig 1) There was no apparent difference with respect to S T response

Hemodynamic observations at rest in supine and sitting positions and during exercise are summarized in Table II significant differences

*See Table I for definitions.

Table I Physical and clinical data on normal middle aged women

	Postexertional S-T response		
	–	+	*Total*
No	6	4	10
Age (yr)	51 ± 6	56 ± 4	53 ± 6
Height (cm)	161 ± 4	165 ± 5	163 ± 4
Weight (kg.)	60 5 ± 6 5	67.2 ± 4 6	63 4 ± 4 3
Relative weight (%)	102 ± 15	109 ± 9	105 ± 13
Capacity at rest (ml /L.)	180 ± 15	180 ± 11	180 ± 13
Hematocrit (%)	37 ± 3	35 ± 1	36 ± 3
Potassium (mEq /L.)	4 20 ± 0 18	4 13 ± 0.28	4 17 ± 0 21
Resting systolic blood pressure (mm. Hg)†	136 ± 19‡	163 ± 6§	148 ± 20
Resting diastolic blood pressure (mm Hg)†	78 ± 11‡	82 ± 6	80 ± 9
Resting heart rate (beats/min)†	[illegible] ± [illegible]	80 ± 12	80 ± 15
Activity status			
Active	1	0	1
Sedentary	5	4	9
Smoking	0	0	0
Drugs taken at time of testing (prescribed by own physicians)			
Thyroid hormone	3	1	4
Tranquilizers	0	1	1
Estrogens	0	2	2
Diuretics	1	0	1
Antihistamines	2	0	2

Relative weight = observed weight/predicted weight × 100, where predicted weight in kilograms = −68 2 + 0.79 (height in centimeters)
t first examination
†During hemodynamic study with catheter
‡No = 5
§$P < 0.03$

for the several observations during exercise are shown in Fig. 2.

Arterial oxygen contents during exercise increased progressively with intensity of work The ST negative group showed a 7 per cent increase (174 ml per liter at rest to 186 ml per liter during exercise) The ST positive group showed a 9 per cent increase from a lower resting value in arterial oxygen content (170 ml. per liter at rest to 186 ml per liter during exercise)

There were no differences between the two groups in mean heart rate stroke volume cardiac output and A V O_2 D either at rest or during exercise

At rest both supine and sitting as well as during the last five minutes of exercise mean systemic arterial pressure was higher in the ST positive group (Figure 2) Tests for equality of

Elevated arterial pressure and postexertional ST-segment depression in middle-aged women

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The greater prevalence of 'false positive' ST-segment depression after exercise in women than in men, in persons over 40 years of age, or in asymptomatic persons with hypertension has been described by several investigators over the past 25 years [1-7] Over an 8 year interval, Åstrand[3] found that the prevalence and the severity of this response increased, particularly in women with hypertension Profant and associates[6] reported ST segment depression in 33 per cent of 144 healthy middle aged women (only 18 per cent by computer analysis), the prevalence doubling in overweight subjects, those with hypercholesterolemia (over 270 mg per 100 ml), and in those with systolic pressure exceeding 140 mm Hg Cumming and associates[7] reported that the prevalence of ST segment depression among 357 women free of cardiovascular disease was up to 25 per cent of women 20 to 39 years 50 per cent of women 40 to 59 years, and 60 per cent of women over 60 years They concluded that exercise ECG changes were unreliable for screening or diagnosis of coronary artery disease in women

We designed this preliminary study to define normal hemodynamic responses of healthy middle aged women to graded levels of exercise up to maximum, in the upright posture as a basis for evaluating such responses of women with coronary heart disease Fortuitously, some subjects exhibited both ST segment depression and significant elevations in arterial pressures, which offers a possible explanation of why some other women have ST segment depression—and even a gna-despite normal arteriograms

Material and methods

Ten healthy women, 43 to 61 years of age and free from symptoms or signs of heart disease were selected in 1974 from a roster of 95 who had been studied longitudinally for changes in maximal exercise performance and measurement of $\dot{V}o_2$ in 1973[8] The clinical data were divided into two groups (Table I) according to the single criterion of ST segment response to maximal exercise Four women exhibited after maximal exercise *upsloping* ST segment depression of 1 mm or more in the bipolar precordial electrocardiogram (ECG) lead CB_5 The remaining six showed no ST segment depression None was studied by coronary arteriography to ascertain possible morphological evidence of coronary vascular disease, because of objections on ethical grounds of a review committee that even the small procedural risk should not be imposed on totally asymptomatic healthy women All subjects were non smokers, eight were taking one or two drugs on a regular basis (see Table I)

Informed consent was obtained from each participant, after explanation of the purpose and methods that involved venous cut down for passage of a Swan Ganz catheter into the pulmonary artery for pressure monitoring and of another catheter inserted percutaneously into the

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FM–1 min		FM		
–	+	–	+	
6	4	6	4	P*
1496	1574	1550	1610	NS
± 241	± 265	± 245	± 212	
94	94	100	100	NS
– 4	± 6	± 0	± 0	
184	185	186	186	NS
± 17	± 10	± 18	± 11	
53	56	50	55	NS
± 12	± 4	± 9	± 5	
131	129	136	131	NS
± 13	± 9	± 13	± 9	
11.3	11 8	11 5	12 3	NS
± 1 1	± 1 5	± 0 8	± 1 0	
167	168	181	176	NS
± 19	± 5	± 16	± 7	
68	0	64	69	NS
± 9	± 8	± 5	± 4	
115	132	117	135	< 0 001
+ 13	± 20	± 16	± 22	
21	[illegible]	22	33	< 0 001
– 8	± 6	± 8	± 4	
814	906	815	874	< 0 05
± 96	± 183	± 127	± 121	
144	200	149	213	< 0 001
± 48	± 61	± 52	± 29	
186	272	208	236	< 0 05
± 22	± 6	± 31	± 46	
6.7	4 7	6 6	4 1	< 0 001
± 2.3	± 1 1	± 2 5	± 0 6	

n the ST negative group than in the ST positive group (See Table III)

Definitions

M, the spatial magnitudes of the heart vectors.
MP the spatial magnitude of the maximum P vector
M_{qrs} the QRS complex in the M tracing
M_{st} the ST-segment in the M tracing
MR the spatial magnitude of the maximum QRS vector R
MT the spatial magnitude of the maximum T vector T
MS the spatial magnitude of $\hat{S}$ the vector at the end of M_{qrs} (MS is frequently zero)
ST the vector occurring at the midpoint in time between $\hat{S}$ and $\hat{T}$
IR the vector occurring at the instant when the area under M is half its final value
the vector occurring 5 msec after IR
PA latitude tracing the tracing of the posteroanterior directions of the heart vectors
θ the angle subtended in space between $\hat{st}$ and a defined reference direction, β 50A + 30 at rest or 50A + 20 after exercise
α-longitude tracing the tracing of the directions in the frontal plane of the heart vectors.

At the initial minute of recovery after maximal exercise the most impressive differences were observed in MS θ and $\hat{ST}$ α longitude MS θ exceeded the ischemic criterion of ≥ 10 6 mV ° and was 4 3 times as great in the ST positive group as in the ST negative group $\hat{ST}$ and $\hat{T}$ α longitudes were rotated leftward to negative values in the ST positive group MT was higher in the ST negative group than in the ST positive group

At one minute of recovery higher MP and MT together with lower MR were observed in the ST negative than in the ST positive group S T slope was also much greater in the ST negative group than in the positive

At the third minute of recovery the trend of lower MR and higher MT in the ST negative group than in the ST positive group was also observed. T PA latitudes also differed in the two groups The ST negative group showed lower $\hat{T}$ PA latitude than the ST positive group

Discussion

The most impressive differences in responses to maximal exercise in these healthy middle aged women are the significantly elevated mean pulmonary and systemic arterial pressures during exercise in the four who exhibited asymptomatic postexertional upsloping ST segment depression Inasmuch as the pressures were elevated at each stage of exercise the average differences in total number of measurements were significant

Because depression of at least 1 mm of an upsloping ST segment may be interpreted as functional evidence of an imbalance between coronary arterial supply and myocardial demand for oxygen it is also important to consider other confounding variables that may contribute to this response Incidental treatment with drugs prescribed by their physicians for divers reasons needs to be considered Of four who had been taking thyroid prescriptions three had a normal and one had a positive ST response (Table I) Inasmuch as tranquilizers may be implicated in ST segment depression after exercise [9] it was noted that one woman was receiving such medication at the time of the study Whether estrogen therapy contributed to a positive ST response because of fluid retention and expansion of plasma volume cannot be ascertained from a single observation There was no evidence of anemia or hypokalemia as contributory factors and all were nonsmokers.

Table II Hemodynamic responses at rest and during exercise (mean ± S D)

Postexertional S T response	Rest				Exercise					
	Supine		Sitting		FM–4 min		FM–3 min		FM–2 min	
	−	+	−	+	−	+	−	+	−	+
No	6	4	6	4	6	4	6	4	6	[illegible]
V_{O_2} (ml /min)†	200 ± 34	226 ± 13	280 ± 46	267 ± 35	1 112 ± 224	1 104 ± 205	1 281 ± 231	1 235 ± 263	1 400 ± [illegible]	[illegible]
% V_{O_2} max	12 ± 3	13 ± 2	18 ± 5	16 ± 3	70 ± 8	68 ± 7	80 ± 7	76 ± 7	88 ± 5	[illegible]
$C_{A_{O_2}}$ (ml /L)†	166 ± 13	164 ± 10	174 ± 13	170 ± 8	181 ± 15	178 ± 8	182 ± 15	180 ± 8	18[illegible] ± 16	[illegible]
$C_{V_{O_2}}$ (ml /L)†	127 ± 21	121 ± 7	116 ± 16	119 ± 7	63 ± 9	69 ± 10	57 ± 10	64 ± 8	57 ± 12	[illegible]
A V_{O_2} D (ml /L)	39 ± 9	44 ± 9	58 ± 6	51 ± 7	118 ± 9	110 ± 14	124 ± 10	117 ± 11	124 ± 13	[illegible]
Q (L /min)	5 7 ± 3 1	5 3 ± 1 2	4 9 ± 1 1	5 3 ± 1 2	9 3 ± 1 2	10 1 ± 1 3	10 2 ± 1 1	10 5 ± 1 4	11 2 ± 1 0	[illegible]
HR (beats/min)	84 ± 19	76 ± 13	84 ± 18	80 ± 12	138 ± 24	132 ± 7	150 ± 21	145 ± 6	160 ± 18	[illegible]
SV (ml)	67 ± 20	70 ± 9	59 ± 12	65 ± 6	68 ± 10	76 ± 9	69 ± 8	72 ± 8	71 ± 10	[illegible]
$\bar{P}_{SA}$ (mm Hg)‡	99 ± 9	113 ± 10	100 ± 13	116 ± 8	107 ± 14	125 ± 11	111 ± 18	128 ± 13	11[illegible] ± 10	[illegible]
$\bar{P}_{PA}$ (mm Hg)	17 ± 7	17 ± 7	12 ± 5	15§ ± 8	18 ± 6	23 ± 3	19 ± 7	24 ± 3	[illegible]0 ± 7	[illegible]
$\bar{R}_{SA}$ (dyn cm sec⁻⁵)‡	1 819 ± 527	1 768 ± 160	1 628 ± 540	1 816 ± 362	910 ± 101	1 007 ± 162	866 ± 114	972 ± 14[illegible]	805 ± 84	[illegible]
$\bar{R}_{PA}$ (dyn cm sec)	274 ± 127	279 ± 160	206 ± 91	266§ ± 138	152 ± 38	168 ± 45	147 ± 47	188 ± 44	139 ± 44	[illegible]
PR/100‡	75 ± 12	86 ± 18	76 ± 12	92 ± 17	141 ± 35	164 ± 9	160 ± 41	183 ± 15	1[illegible]3 ± 26	[illegible]
$P_{SA}/\bar{P}_{PA}$‡	6 5 ± 3 9	7 0 ± 1 7	9 9 ± 2 5	10 1§ ± 6 4	6 3 ± 1 7	5 4 ± 0 7	6 7 ± 1 6	5 3 ± 0 6	6 6 ± 1 8	[illegible]

Tested for quality of regression lines coefficient for last 5 minutes of exercise
†Some data missing between FM–4 min and FM–2 min were obtained from regression equation for all other exercise data of each individual, 80 per cent coefficients of correlation were above 0 900
‡N = 5 for ST negative group (in one subject arterial pressures could not be obtained)
§N = 3 (in one subject mm Hg reference line lost)
Abbreviations A V O D = arterial-mixed venous oxygen difference C_{A_O} = arterial oxygen content Cv_{O_2} = venous oxygen content HR = heart rate $\bar{P}_{PA}$ = mean pulmonary arterial pressure $\bar{P}_{SA}$ = mean systemic arterial pressure PR = pressure rate product $\dot{Q}$ = cardiac output $\bar{R}_{PA}$ = mean pulmonary arterial resistance $\bar{R}_{SA}$ = mean systemic arterial resistance SV = stroke volume Vo = oxygen uptake

regression coefficients[14] during the final five minutes of exercise showed that the ST positive group had significantly higher pressure responses in both systemic ($P < 0\,001$) and pulmonary arteries ($P < 0\,001$) Thus the ST positive group had higher pressure rate products (mean systemic pressure times heart rate) than those of the ST negative group, particularly during the final minute of exercise ($P < 0\,01$) The systemic and pulmonary resistances were also significantly higher in the ST positive group ($P < 0\,001$)

The relationship between the ratio of mean systemic to mean pulmonary pressure ($P_{SA}/\bar{P}_{PA}$) and cardiac output differed between the two groups The ST negative group maintained this ratio as cardiac output increased with exercise while in the ST positive group this ratio fell during the final 4 minutes of exercise because of the greater increase in mean pulmonary pressure ($P < 0\,001$)

Salient differences by polarcardiographic analysis during rest and in recovery are shown in Table III

At rest ST spatial magnitude (M_{ST}) was higher

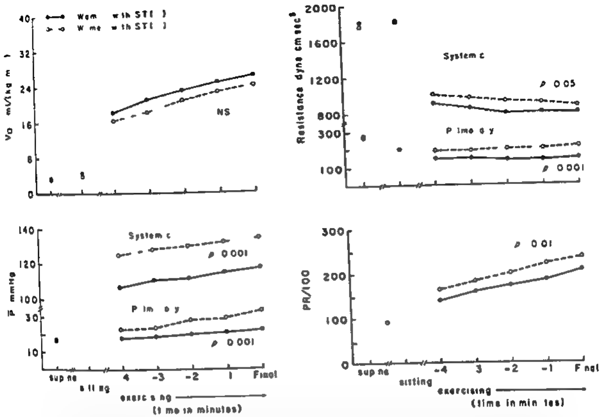

Fig 2 Time course of oxygen uptake arterial pressures and resistances and pressure-rate product at rest and during exercise. Note higher values of pressures and their derivatives in women who exhibited postexertional S-T depression Arterial pressure was recorded only in five of the six ST negative women so that n = 6 in the upper left panel and n = 5 in the other three panels N = 4 for ST positive women throughout. Each value is the mean of five observations.

of an overloaded left ventricle Further evidence of such functional ischemia is provided by the quantitative polarcardiographic changes observed in these four women These included lower spatial magnitude of ST at rest and leftward rotation of ST and T α longitudes lower spatial magnitudes of T and an increase in MS following exertion[11] Furthermore the st T slopes were reduced after exercise [2]

Unlike men with symptomatic coronary artery disease which restricts arterial supply of oxygenated blood and limits both maximal oxygen uptake and cardiac output responses to and particularly of maximal exercise there was no difference in either $V_{O_{2m}}$ or Q_m in these four ST positive women Nor was there any reduction in arterial O_2 content

Lacking evidence of impaired arterial supply of O_2, the ECG evidence of myocardial ischemia is more likely to be related to increased myocardial demand for O particularly at the subendocardial layer Kitamura and associates[15] and more recently Nelson and associates demonstrated high correlations between the product of systolic arterial pressure and heart rate and either coronary blood flow or myocardial oxygen consumption in normal men during exercise Thus the pressure rate product can be used as an index of myocardial oxygen demand Since mean arterial pressures were higher ($P < 0.001$) in both pulmonary and systemic circulations in these four women the imbalance between supply and demand is probably largely attributable to greater preload and afterload imposed on an otherwise normal left ventricle This is also consistent with observation of ST segment depression in asymptomatic middle aged men who achieved postmaximal exercise performance relative to their ST negative peers as reported by Kasser and Bruce

It is also of interest to note that in the initial testing of 1 346 asymptomatic healthy middle

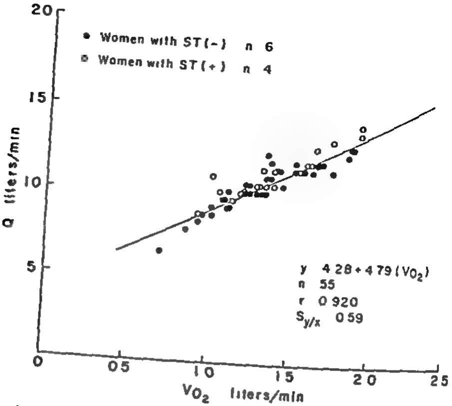

Fig 1 Relationship of cardiac output to oxygen uptake during graded levels of exercise Note high correlation and normal coefficients for regression equation

Table III Polarcardiographic analysis of P R st ST T vectors in 10 normal middle aged women (salient differences* only)

	ST negative (n = 6) Mean ± SD	ST positive (n = 4) mean ± SD
Rest sitting		
M_{ST} (mV)	0 14 ± 0 04	0 05 ± 0 02
Recovery 0 min		
MS (mV)	3 6 ± 1 8	15 6 ± 4 8
ST α longitude (°)	30 ± 53	−133 ± 21
MT (mV)	0 58 ± 0 16	0 33 ± 0 11
$\hat{T}$ α longitude ( )	33 ± 10	−50 ± 41
Recovery 1 min		
MP† (mV)	0 26 ± 0 04	0 20 ± 0 03
MR (mV)	1 25 ± 0 39	1 83 ± 0 20
MT (mV)	0 63 ± 0 11	0 46 ± 0 03
$\hat{st}$ $\hat{T}$ slope (mV /ms)	6 24 ± 1 86	3 82 ± 0 58
Recovery 3 min		
MR (mV)	1 29 ± 0 24	1 80 ± 0 22
MT (mV)	0 50 ± 0 13	0 33 ± 0 06
$\hat{T}$ PA latitude ( )	31 ± 20	58 ± 13

*$P < 0.05$ in all instances

†MP the spatial magnitude of the maximum P vector $\hat{P}$ (see text footnote for other definitions)

The important point in this study is not identification of exact causes of ST segment depression, but rather the common denominator of moderate but significant elevations of pulmonary and systemic pressures associated with exercise in the subjects who manifested this ECG response but showed neither evidence of reduced cardiac output or oxygen uptake nor any decrease in arterial oxygen content Thus the associated hemodynamic changes which could augment both the preload and the afterload on the left ventricle were not accompanied by the usual functional manifestations of significant coronary artery disease

The importance of the ischemic configuration of flat or sagging ST depression, now called horizontal or downsloping and persisting for 2 to 4 minutes after exercise was emphasized by Mattingly[16] as the most reliable finding, this was further corroborated by Robb and Marks[17] in a follow up study of 800 cases of upsloping ST segment depression after the double Masters two step test in male life insurance applicants, who considered this to be a normal response to exercise Nevertheless the presence of an upsloping response may represent functional imbalance between coronary supply of oxygenated blood and excessive metabolic requirement

Niederberger M. W and Meilink, L. J Ischemic polar cardiographic changes induced by exercise A new criterion, Circulation 58 725 1973

Neiderberger M Bruce, R. A., Dower G E and Hofer V Influence of age and ischemic heart disease on spatial ST T magnitudes at rest and after maximal exercise J Electrocardiol. 6 279 1973

McDonough, J R., Danielson, R. A Wills, R. E., and Bine, D L. Maximal cardiac output during exercise in patients with coronary arterial disease Am J Cardiol. 33 23, 1974.

Acton, F S Analysis of straight line data New York, 1966, Dover p. 172.

Linhart, J W Laws, J G., and Satinsky J D Maximum treadmill exercise electrocardiography in female patients, Circulation 60 1173 1974

Mattingly T The post-exercise electrocardiogram Its value in the diagnosis and prognosis of coronary arterial disease, Am. J Cardiol. 9 395 1962

Robb, G P and Marks, H. H Postexercise electrocardiogram in atherosclerotic heart disease J A M A. 200 918, 1967

Kitamura, K., Jorgenson C R Grobel, F L. Taylor H. L., and Wang Y Hemodynamic correlates of myocardial oxygen consumption during upright exercise J Appl. Physiol. 32 516, 1972.

19 Nelson, R., Gobel, F L. Jorgenson C R. Wang, K., and Taylor H. L. Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise Circulation 50 1179 1974

20 Kasser I. S., and Bruce R. A. Comparative effects of aging and coronary heart disease on submaximal exercise Circulation 39 759 1969

21. Chiang, B. N., Alexander R., Bruce R A Thompson H J and Ting, N Factors related to ST segment depression after exercise in middle-aged Chinese men Circulation 40 315 1969

22. Bruce, R. A., Pao Y 1., Ting, N., Chiang B N Li, Y b., Chiang, S. T., Alexander E. R Beasley R P., and Fisher L. D Seven year follow up of cardiovascular study and maximal exercise testing of Chinese men Circulation 51 890 1975

23. Bruce, R. A., Fisher L. D., Cooper M N., and Gey G H *Separation of effects of cardiovascular disease* and age on ventricular function with maximal exercise Am J Cardiol. 34 757 1974

American

aged Chinese men from a population with unusually low prevalence of coronary heart disease 94 who showed ST segment depression after maximal exercise were older and had higher systemic arterial pressures than those without ST segment depression [21] Indeed the prevalence of this response was four times higher in men with elevated blood pressure at rest These distinctions, plus that of being slightly heavier, were still present when 80 men were retested about 7 years later [22]

It may be that minor changes in ventricular function, whether in systolic contraction or in diastolic relaxation in relation to slightly older age contribute to this imbalance Because of the repeatedly documented greater prevalence of postexertional ST segment depression in women than in men, which increases with age with greater body weight with hypercholesterolemia and with elevation of the systolic blood pressure,[1 7] a more appropriate criterion for diagnosis of abnormal ST segment depression after maximal exercise in women should be at least −0 12 mV Even then, this response may be due either to restricted coronary arterial blood flow or to excessive hemodynamic load on the left ventricle, possibly in association with other changes in ventricular function in relation to age The major distinction whether or not chest pain (angina pectoris) occurs is whether the amount and duration of exertion required to elicit ST segment depression are distinctly reduced, as in patients with significant coronary vascular disease, or are within the normal range Other aids to diagnostic interpretation at least in respect to men, are the reduced levels of maximal heart rate maximal systolic blood pressure and pressure rate product at maximal exercise [23]

Summary

Of ten healthy women 43 to 61 years of age four exhibited 1 mm or more of upsloping ST segment depression after maximal exercise, using the Bruce multistage treadmill protocol, the other six did not Cardiac output (direct Fick) was not different in the two groups, either at rest or during exercise The women with ST positive responses were older (56 vs 51 years) and heavier (relative weights 109 per cent vs 102 per cent) and their resting mean systemic pressures were higher Their systemic and pulmonary mean arterial pressures during the last five minutes of upright exercise were significantly higher (P < 0 001) than those in the ST negative group Although the ratio of systemic to pulmonary mean arterial pressures was higher at rest, it progressively fell during exercise in the ST positive group Polarcardiographic display of the Frank ECG during the first 3 minutes of recovery after maximal exercise showed significant differences between the ŜT and T of the two groups After initial recovery, MS θ greatly exceeded 10 mV ° which is a sensitive PCG ischemic exercise criterion in the ST positive group Although the number of observations is limited, it is concluded that greater hemodynamic stress imposed on the subendocardium by elevated pressures, rather than by any significant functional evidence of restriction in coronary blood flow, probably explains much of the postexertional ST segment depression after maximal exercise

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REFERENCES

1 Astrand I Exercise electrocardiograms recorded twice with an 8 year interval in a group of 204 women and men 48-63 years old Acta Med Scand 178 27 1965
2. Leeds, M F and Kroopf S [illegible] Exercise test in electrocardiography Detection of coronary artery disease, California Med 79 36 1953.
3 Davies, F W Jr Scarborough W R Mason R E Singerwald M L and Baker [illegible] M Jr Effects of exercise and smoking on electrocardiograms and ballistocardiograms of normal subjects and patients with coronary artery disease AM HEART J 46 529 1953
4 Schlens, L Sandberg A A Wener J Dvorkin ... and Master A M Effects of single and double two-step exercise tests upon electrocardiograms of 200 normal persons, J Mt. Sinai Hosp 17 242, 1950
5 Lepeschkin E and Surawicz B Characteristics of true-positive and false positive results of electrocardiographic Master two step exercise tests N Engl J Med 258 511, 1958
6 Profant, G R Early R G Nilson K L, Kusumi F Hofer V and Bruce R. A Responses to maximal exercise in healthy middle aged women J Appl. Physiol 33 595 1972
7 Cumming G R Dufresne C., and Samm J Exercise ECG changes in normal women Can Med Assoc. J 109 108 1973
8 Voigt A E Bruce R A Kusumi F Pettet G ... K. Whitkanack [illegible] and Tapia J Longitudinal variations in maximal exercise performance of healthy sedentary middle-aged women J Sports Med In press, 1975
9 Kusumi F Butts, W C and Ruff W L Superior analytical performance of electrolytic cell analysis of blood oxygen content J Appl Physiol 35 299 1973
10 Bruce R. A Kusumi F and Hosmer [illegible] Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease AM HEART J 85 546 1973
11 Dower G E Bruce R A Pool J Simoons, M L

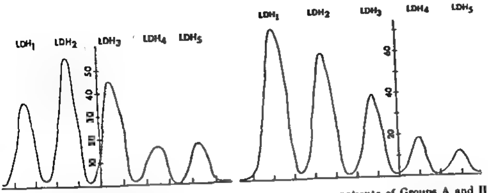

Fig 1 The electrophoretic distribution of the LDH isoenzymes in patients of Groups A and B preoperatively is shown in the left half of the figure the right half is representative of patients in Group A postoperatively

riod, appearance of new Q waves was considered to be significant only when they were of 0 04 second duration or more and/or 25 per cent of the height of the R wave ST segment and T wave changes, although recorded were not considered as evidence for myocardial necrosis Only those supraventricular arrhythmias which were sustained were considered to be significant The ventricular arrhythmias considered to be significant were frequent premature ventricular contractions (more than 10 per minute) multifocal or paired premature ventricular contractions early premature ventricular contractions with R on T phenomenon and ventricular tachyarrhythmias. Other arrhythmias were considered significant when they were associated with a significant drop in blood pressure urine output or change in neurological status Prior experience with patients suffering from classical acute myocardial infarction not related to coronary artery surgery had indicated that the best index of myocardial damage is a change in the LDH LDH, ratio to greater than 1 0 Accordingly the patients were separated in two groups Group A (23 patients) postoperatively demonstrated an LDH LDH, ratio exceeding 1 0 and Group B (50 patients) failed to reveal reversal of the LDH LDH ratio The electrophoretic pattern seen preoperatively and that noted postoperatively in patients of Group A are shown in Fig 1

Results

Preoperative findings There was no significant difference in the mean age male to female ratio family history of coronary heart disease history of hypertension hyperlipidemia or smoking between the two groups (Table I) Similarly ECG evaluation failed to document any significant difference between the two groups regarding the incidence of normal ECG existence of previous myocardial infarction conduction defects or ST segment and T wave changes (Table II) Preoperative angiographic and hemodynamic findings were also similar in both groups as shown in Table III The comparative incidences of patients with elevated left ventricular end diastolic pressure patients with one two or three vessel

Table I Preoperative clinical findings

	Group A 23 patients		*Group B 50 patients*	
	No	*%*	*No*	*%*
Mean age (yr)	56		54	
Male	19	83	43	86
Female	4	17	7	14
Family history of CHD	18	78	36	72
Hypertension	7	30	16	32
Hyperlipidemia	13	57	22	44
Smoking	18	78	36	72

Table II Preoperative ECG findings

	Group A 23 patients		*Group B 50 patients*	
	No	*%*	*No*	*%*
Previous MI	6	26	10	20
Conduction defect	1	4	2	4
ST segment and T wave changes	10	43	22	44
Normal	6	26	16	32

LDH isoenzymes and myocardial infarction in patients undergoing coronary bypass surgery An excellent correlation

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Diagnosis of myocardial infarction in patients undergoing coronary bypass surgery is difficult (1) because of the absence of the usual clinical presentation and (2) the elevated serum enzymes which are commonly used in making the diagnosis of myocardial infarction may be due to the surgical trauma The appearance of new and diagnostic Q waves although highly suggestive of myocardial necrosis has been thought by some to be due to other factors[1] The purpose of this study is to evaluate the efficacy of serum lactic dehydrogenase (LDH) isoenzymes measurements specifically the elevation of LDH_1 in the evaluation of myocardial necrosis during and immediately after coronary artery surgery

Material and methods

Seventy three consecutive patients undergoing coronary bypass surgery at the Creighton Memorial St Joseph Hospital, Omaha Neb were studied The criterion for selection of the patients to be included in this study was that the patient be undergoing coronary bypass surgery without other surgical procedures such as prosthetic valvular replacement, left ventricular aneurysmectomy, or correction of congenital heart defects In this series, patients with prosthetic valvular replacement were not included since the often associated hemolysis may change the LDH_1 LDH_2 ratio Three patients who died on the day of surgery were excluded from this prospective study All patients underwent a complete clinical hemodynamic, and angiographic evaluation Left ventricular end diastolic pressure of 1? mm Hg or above was considered abnormal Angiographic e idence of lumen occlusion exceeding 50 per cent was indicat ve of significant coronary artery disease In these 73 patients the following observations were made preoperatively and on the first second, and third postoperative day (1) Twelve lead electrocardiograms (ECG s) (2) serum glutamic oxyloacetic transaminase (SGOT) (3) serum lactic dehydrogenase (LDH) (4) serum creatinine phosphokinase (CPK) and (5) LDH isoenzyme measurements Serum SGOT LDH and CPK were estimated by standard techniques LDH isoenzymes were electrophoretically separated and stained with tetrazolium blue and their intensities quantitated by a scanning densitometer The observations were continued for an additional 10 days in those patients with abnormal ECG s or abnormal LDH isoenzymes during the postoperative days All ECG, angiographic, and hemodynamic studies were interpreted without the knowledge of the postoperative course or the serum enzyme studies In 20 patients data were available regarding the hemolysis immediately after the bypass and on the third hospital day In the postoperative

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) per cent. [4] Investigators who have used post perative elevations of SGOT and total LDH ave reported the incidence of myocardial infarc on from 10 per cent[5] to as high as 40 per cent.[6] The diagnostic value of new Q waves appearing in the postoperative period has been questioned as they may be due to hypothermia,[7] severe meta olic acidosis, shock,[8] cross clamping of the orta,[7] or the unmasking of an old infarct.[7] Strict riteria of significant Q wave appearance may lso underestimate the incidence of significant myocardial necrosis. Enzyme data using total LDH, SGOT, and CPK have also been questioned as these may not be specific enough to permit the diagnosis of acute myocardial infarction in a given patient following cardiac surgery.[9, 1] Some investigators have considered the postoperative enzyme elevation to be a consequence of cardio pulmonary bypass.[11] Other methods for assess ment of myocardial injury after coronary artery surgery include vectorcardiographic evaluation,[2] measurement of myocardial fraction of CPK (CPK MB)[13] and angiographic documentation of the areas of left ventricular asynergy.[7] Angio graphic evaluation, which is probably a useful technique in long term follow up, is of little use in the diagnosis or management of myocardial infarction occurring in the immediate postopera tive period. The presence of CPK MB, although highly suggestive of myocardial injury, may not be specific enough. In one study[13] 77 per cent of patients undergoing coronary artery surgery demonstrated presence of this enzyme in the immediate postoperative period. The same study was unable to correlate the presence of CPK MB with postoperative arrhythmias or appearance of other complications such as congestive heart failure or shock. The results of our study indicate that there is a close and statistically significant relationship between the appearance of Q waves and reversal of the LDH, LDH, isoenzyme ratio. The incidence of serious complications such as life threatening arrhythmias, severe congestive heart failure, and signs and symptoms of shock was also significantly higher in patients in whom the LDH, LDH, ratio was reversed. These data would suggest that patients in Group A had suffered from significant myocardial necrosis. Our results also indicate that maximum elevations of CPK, SGOT, and total LDH were not reliable criteria to establish a postoperative diagnosis of myocardial infarction. In addition to myocardial necrosis, other factors may contribute to the reversal of LDH, LDH, ratio such as myocardi tis,[1] renal corticol infarction,[15] and hemolytic anemias of any cause.[4] Cardiomyopathy and renal infarction were not present in the patients of this study. Some degree of hemolysis following cardiopulmonary bypass was noted as indicated by mild elevation of plasma hemoglobin immedi ately postoperative (Table VII) but had returned to normal range by the third postoperative day when the change in LDH, LDH, ratio was most apparent. LDH, LDH, ratio is unaffected by pericarditis,[1] tachyarrhythmia,[4] pulmonary em boli,[1] electrical cardioversion, or cardiac cathe terization, complications and procedures so frequently associated with cardiac surgery.

The reasons for the occurrence of myocardial infarction in patients undergoing coronary artery bypass surgery may be many. They vary from technical mishaps to closure of the saphenous vein grafts[21] or occlusion of the bypassed vessel proximal to the graft, or occlusion of other diseased vessels not bypassed. Intra or postop erative myocardial infarction adds significantly to the morbidity of coronary artery bypass surgery and its recognition becomes clinically important because of the frequently associated life threatening arrhythmias and/or left ventric ular failure. The postoperative management with regard to ambulation and convalescence is like wise different from the management of those patients without intra or postoperative infarc tion. There were no deaths in patients suffering from postoperative myocardial infarction in this study, a fact which has also been noted by other investigators. High percentage of fatalities in acute myocardial infarction occur in the pre hospital phase and it is possible that immediate recognition and treatment of complications in those patients who are very carefully monitored may be responsible for the low mortality rate. Long term effects of myocardial necrosis in those patients are still undetermined as our observation time has been rather limited. A long term follow up and comparison of patients who do not suffer postoperative myocardial infarction with those who do will be certainly indicated.

Previous studies in classical acute myocardial infarction have shown that in absence of signifi cant hemolysis increased LDH activity is the most sensitive index of myocardial necrosis. The results of our study indicate that the reversal of

Table III Preoperatıve angıographıc hemody namıc findıngs

	Group A 23 patıents		Group B 50 patıents	
	No	%	No	%
LVEDP				
One vessel dısease	5	22	13	26
Two vessel dısease	9	39	22	44
Three vessel dısease	7	30	18	36
Collaterals present	7	30	10	20
	14	61	36	72

Table IV Surgıcal procedure

	Group A 23 patıents		Group B 50 patıents	
	No	%	No	%
One vessel saphenous veın bypass graft	14	61	25	50%
Two vessel saphenous veın bypass graft	8	36	18	36
Three vessel saphenous veın bypass graft	1	4	3	6

Table V Postoperatıve course and ECG findıngs

	Group A 23 patıents		Group B 50 patıents		
	No	%	No	%	P
New Q waves	18	78	1	2	< 0.001
Sıgnıficant arrhythmıas	16	70	7	14	< 0.001
Severe CHF and/or shock	9	39	0	0	< 0.001

dısease and patıents wıth demonstrable collater al cırculatıon were sımılar between groups

Postoperatıve findıngs All patıents underwent aortocoronary saphenous veın bypass graft, ın none of the patıents dıd pump tıme exceed 2 hours there was no dıfference between groups as to the number of vessels bypassed (Table IV) Postoperatıve ECG findıngs were sıgnıficantly dıfferent ın two groups (Table V) In Group A (ı e those wıth reversed LDH ısoenzymes) 18 of 23 patıents (78 per cent) developed sıgnıficant new Q waves, ın Group B thıs occurred ın only one patıent Sıgnıficant arrhythmıas occurred ın 70 per cent of patıents ın Group A as compared to only 14 per cent ın Group B Severe congestıve heart faılure and/or symptoms of shock occurred

Table VI Maxımum postoperatıve enzyme cha[nges]

	Group A	Group B
Total LDH	240 ± 28	230 ± 19
Total CPK	80 ± 30	85 ± 25
Total SGOT	50 ± 25	40 ± 18
Normal LDH	40-100 units	
Normal CPK	0-[illegible]0 units	
Normal SGOT	0-17 units	

Table VII Plasma hemoglobın

Immedıately after surgery (20 patıents)	
Group A (9 patıents)	28 ± 1[illegible]
Group B (11 patıents)	[illegible] ± 1[illegible]
Thırd day postoperatıve (20 patıents)	
Group A (9 patıents)	8 ± 6
Group B (11 patıents)	10 ± 4

ın 39 per cent of Group A patıents but ın none ın Group B It should be noted that the seven patıents ın Group A who developed symptoms of severe congestıve heart faılure or shock had trıple vessel coronary artery dısease In most of the patıents ın Group A LDH reversal occurred on the thırd postoperatıve day (78 per cent) and the reversal was persıstent for 10 days LDH ısoenzyme reversal dıd not occur ın one patıent who dıd have sıgnıficant Q waves ın Group B There were no deaths ın eıther Group A or B The maxımum elevatıons of total LDH, CPK and SGOT postoperatıvely were not sıgnıficantly dıfferent between groups (Table VI) Plasma hemoglobın levels on the day of surgery and thırd postoperatıve day were sımılar ın the two groups (Table VII) In our study, usıng the strıct crıterıa of sıgnıficant new Q wave appearance myocardıal ınfarctıon rate ıs 24 5 per cent, whereas reversal of LDH_1 LDH_2 ratıo crıterıon ıncreases the ıncı dence to 31 per cent If we ınclude the three patıents who dıed on the day of surgery the mortalıty rate ın thıs study group ıs 4 per cent

Dıscussıon

Myocardıal ınfarctıon documented by the appearance of sıgnıficant Q waves ın patıents undergoıng coronary artery bypass surgery has been reported by several ınvestıgators The ıncı dence varıes from as low as 7 per cent to as hıgh as

xperimental and laboratory reports

ffects of unilateral stellate ganglion blockade on the rrhythmias associated with coronary occlusion

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oronary arterial occlusion (CAO) is accompanied by either an increase in cardiac sympathetic neural discharge elicited by baroceptive or ardio-cardiac reflexes[1, 2] or vagally mediated ecreased cardiac sympathetic activity.[3] CAO is lso associated with cardiac arrhythmias which re greatly reduced by bilateral stellectomy lowever the possible consequences of unilateral lterations in cardiac sympathetic tone have been verlooked. Such alterations may emanate from he central nervous system during normal physiological conditions or in pathophysiological states. Unilateral alterations in cardiac sympathetic tone for instance are thought to be the rigin of the long Q T syndrome.[6] This is a clinical condition characterized by electrocardiographic (ECG) abnormalities and often fatal ventricular arrhythmias always following emotional or physical stresses probably dependent upon a congenital decrease in right cardiac sympathetic activity.[6]

Electrical stimulation of either stellate ganglion has different effects.[8, 9] Moreover left stellate ganglion stimulation increases the temporal dispersion of recovery or excitability,[9] a factor which facilitates the development of premature ventricular beats and tachyarrhythmias including ventricular fibrillation (VF).[1] It has also been recently reported that arrhythmias are often produced by electrical stimulation of branches of left cardiac sympathetic nerves.[1, 11] In the absence of one stellate ganglion (SG) an increase in sympathetic activity may be equivalent to unilateral stimulation

From these considerations it seemed reasonable to investigate the effects of unilateral alterations in cardiac sympathetic tone upon the genesis of arrhythmias associated with CAO We found that the occurrence of arrhythmias was enhanced by blockade of the right stellate ganglion and reduced by blockade of the left

Methods

Experiments were performed in 33 dogs (15 to 25 kilograms) anesthetized with chloralose (60 mg per kilogram) The animals were ventilated with room air by means of a cuffed endotracheal tube connected to a Harvard respirator In 31 experiments the cervical vagi were cut at the beginning of the experiment One femoral artery was cannulated with a catheter tip transducer (Millar Instruments) which was passed retrograde into the left ventricle and the other with a woven Dacron catheter which was positioned in the descending aorta

The chest was opened on the left side through an incision between the fourth and fifth ribs and the heart was exposed The descending and the circumflex branches of the left coronary artery were dissected free from surrounding tissues and a suture was slipped around them and passed through a piece of polyethylene tubing Care was exercised to avoid damage to the pericoronary nerves during the dissection In other experiments[3] with much more extensive dissection of the coronary vessels the cholinergic and adrener

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LDH_1 LDH_2 ratio maintains similar degrees of sensitivity in patients undergoing coronary artery surgery It is probably one of the best clinical tools for evaluating postoperative myocardial necrosis, because of not only its high sensitivity but also its excellent specificity

Summary

To evaluate the efficacy of LDH isoenzymes in the detection of myocardial infarction in patients undergoing coronary bypass surgery 73 patients were studied pre and postoperatively by ECG CPK, SGOT, total serum LDH, and LDH isoenzyme measurements A reversal of the LDH_1 LDH_2 ratio was considered indicative of myocardial necrosis Accordingly the patients were separated into two groups Group A (23 patients) who demonstrated an LDH_1 LDH ratio exceeding 1 0 and Group B (50 patients) who failed to reveal an LDH_1 LDH reversal The two groups were similar in regard to preoperative evaluation and operative procedure performed The postoperative ECG findings were significantly different In Group A 18 of 23 patients (78 per cent) developed significant new Q waves This occurred in only one patient in Group B Significant arrhythmias occurred in 70 per cent of the patients in Group A as compared to 14 per cent of those patients in Group B Severe congestive heart failure and/or clinical evidence of shock occurred in 39 per cent of Group A patients and in none in Group B The results of our study indicate that the reversal of the LDH_1 LDH_2 ratio is a valuable tool for the evaluation of postoperative myocardial infarction

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REFERENCES

1 Bassan M N Oatfield R Hoffman I Matloff J and Swan H J C New Q waves after aortocoronary bypass surgery (unmasking of an old infarction) N Engl J Med 290 349 1974

2 Alderman F L Matlof H J Wexler L Shumway N E and Harrison D C Results of direct coronary artery surgery for the treatment of angina pectoris N Engl J Med 288 535 1973

3 Kansal S Roitman D Sheffield L B and Kouchoukos N T Acute myocardial injury following aortocoronary bypass surgery Am J Cardiol 33 140 1973

4 Espinoza J Lipski J Litwak R Donoso E and Dack S New Q waves after coronary artery bypass surgery for angina pectoris Am J Cardiol 33 221 1974

5 Rose M R Glassman E Isom O W and Spencer F C Electrocardiographic and serum enzyme changes of myocardial infarction after coronary artery bypass surgery Am J Cardiol 33 215 1974

6 Hultgren H N Miyaga W, Buch W and Angell W W Ischemic myocardial injury during coronary artery surgery Am Heart J 82 624 1971

7 Klein H M Gross H and Rubin I Transient electrocardiographic changes simulating myocardial infarction during open heart surgery Am Heart J 79 463, 1970

8 Shugoll G Transient electrocardiographic changes simulating myocardial infarction associated with shock and metabolic stress Am Heart J 74 402 1967

9 Shirey E K Proudfit W L and Sones F M Jr Serum enzymes and electrocardiographic changes after coronary artery surgery Correlation with selective coronary angiography and left ventriculography Chest 57 122 1970

10 Alderman E L Matlof H J Shumway H E, and Harrison D E Evaluation of enzyme testing for detection of myocardial infarction following direct coronary artery surgery Circulation 48 135 1973

11 Neutze J M Drakeley M J Barratt Boyes B E and Bubbert K Serum enzymes after cardiac surgery using cardiopulmonary bypass Am Heart J 88 425 1974

12 Anderson W F Brundage B H and Cheitlin M D Vectorcardiographic changes following saphenous vein bypass graft (abst) Am J Cardiol 31 116 1973

13 Oldham H N Jr Roe C R Young W G and Dunn, S H Intraoperative detection of myocardial damage during coronary artery surgery by plasma creatinine phosphokinase isoenzyme analysis Surgery 74 917 1973

14 Chohn L and Djordjevich O V Serum lactic dehydrogenase isoenzyme pattern in cardiovascular and other diseases, the particular reference to acute myocardial infarction J Lab Clin Med 64 355 1964

15 Batsakis, J G and Briere R O LDH isoenzymes by urea inhibition and substrate (lactate) modification A clinical evaluation Clin Biochem 2 171 1969

16 Sobel B E and Shell W E Serum enzyme determinations in the diagnosis and assessment of myocardial infarction Circulation 45 471 1972

17 Runde I and Dale J Serum enzymes in acute tachycardia Acta Med Scand 179 535 1966

18 Tatsakis J G and Briere R O Interpretive enzymology Springfield Ill 1967 Charles C Thomas, Publisher

19 Kontiinen A Hapli V Louhija A and Hartel G Origin of elevated serum enzyme activities after direct current countershock N Engl J Med 28 731 1969

20 Michie D D Conley M A Carretta R F, and Booth, R W Serum enzyme changes following cardiac catheterization with and without selective coronary arteriography Am J Med Sci 260 11 1970

21 Balooki H Sommer L S and Ghahramani, A Complications of coronary bypass surgery Circulation 48 III 120 1973

22 Maurer B J Oberman A Holt J H Jr Kouchoukos N T Jones, W B Russell R O Jr and Reeves, T J Changes in grafted and nongrafted coronary arteries following saphenous vein bypass grafting Circulation 50 293 1974

Table I. Effect of right stellate ganglion blockade (RSGB) on the number of ectopic beats associated with coronary arterial occlusion

Exp no.	Trials	Coronary artery occluded (sec)	Control coronary artery occlusions					RSGB coronary artery occlusions				
			Blood pressure†	Heart rate†	Ectopic beats: During	Ectopic beats: After‡	Ectopic beats: Total	Blood pressure†	Heart rate†	Ectopic beats: During	Ectopic beats: After‡	Ectopic beats: Total
1	1 2	Circ (90″)	115-115	1.6-123	0	0	0	110-115	114 102	2	2	4
	3-4	Circ (90′)	100- 90	100- 98	1	1	2	115-105	90 84	[illegible]	[illegible]	4
	5-6§	Circ (90′)	110-115	150-150	[illegible]	0	[illegible]	125-1 0	140-140	3	0	3
2	1 2	Circ (90′)	120- 90	130-126	0	0	0	125-105	130-130	1	2	3
	3-4§	Circ (90′)	130-130	153-150	0	0	0	130-127	144 142	2	1	3
3	1 ?	Desc (45)	140-140	162 162	0	0	0	140-135	146-148	2	0	2
	3-4	Desc (45)	140-130	168-165	1	0	1	155-150	138-138	2	[illegible]	2
	5-6	Desc + circ (30′)	165-140	148-159	0	0	0	165 145	132 132	3	0	3
	-8	Desc + circ (45)	165 145	148-160	0	0	0	165 135	132 140	2	1	3
	9-10	Desc + circ (5)	165-145	148-165	1	0	1	165-130	13? 144	4	3	7
	11 12	A (30′) + desc + circ (.5)	165 160	144 147	0	[illegible]	0	165-115	132 156	11	7	18
	13-14	A (30′) + desc + circ (75)	165-165	140-144	0	1	1	165-115	132 144	13	3	16
4	1 2	Desc + circ (30′)	150-120	186-184	0	0	0	130-110	165-177	4	0	4
	3-4	Desc + circ (30′)	135-115	174 180	0	0	0	130-110	1.9-1.6	0	1	1
	5-6	Desc + circ (30′)	135- 90	180-186	0	0	0	130- 90	162 162	2	0	2
5	1 2	Circ (30′)	155-155	210-210	0	0	[illegible]	160-160	190-186	5	[illegible]	5
	3-4	Circ (30′)	175-175	212 212	0	0	0	1.5-175	212 ?12	0	7	7
6	1 2	Circ + desc (?0′)	195-185	222 222	1	0	1	190-150	190-186	8	43	51
	3-4	Circ + desc (20″)	200-150	222 234	6	2	8	195-160	180-180	18	57	?5
	5-6	Circ + desc (?0)	200-180	234 232	3	0	3	210 1.0	180-180	10	0	10
	-8	Circ + desc (20′)	200-140	234 230	4	5	9	210-145	1?2 183	5	38	[illegible]
7	1 2	Desc (10′)	120-120	174 174	2	0	2	120-125	156-159	4	2	6
	3-4	Desc (10′)	115-1 0	180-180	0	0	0	115-120	180-180	3	1	4
	5-6	Desc (10′)	120-120	180-180	1	0	1	125 120	180-180	[illegible]	0	5
8	1 2	Circ (10)	115-110	198-192	1	1	[illegible]	110-100	180-180	14	1	15
	3-4	Circ (10″)	105-100	192-192	1	0	1	95 90	1.5-1 5	3	1	4

*Change from control significant, p < [illegible]005
†Values at beginning and end of occlusion.
‡"After" is the 60 sec immediately following release of occlusion.
§After ... tomy
‖During atrial pacing.
¶A respirator stopped fo 30 sec preceding the CAO

observed and 15 animals (Group III) were discarded from the study

The effects of CAO on HR and BP were usually dependent on the length of the occlusion itself Decreases in BP when present were accompanied by increases in HR which were reduced during right SGB (Table I)

A. Effects [illegible] cold blockade of stellate ganglia

1 Right stellate ganglion blockade The main changes we observed were on ECG and heart rate (HR) After 60 to 90 seconds of cooling the HR dropped 20 to 45 b p m This reduction in HR is a reliable index of an effective right SGB after vagotomy The T wave often became more positive and the corrected Q T interval always increased The P R interval was usually unmodified

2 Left stellate ganglion blockade The changes during left SGB were minor BP and maximum dP/dt were usually slightly decreased (5 to 10 per cent) HR was unaffected or slightly increased The most consistent ECG change was a reduction in T wave positivity or even the appearance of a negative T wave The Q T and P R intervals were essentially unaltered

B Results in Group I animals The control values of BP and HR at the beginning of these 11

gic innervation was found to be intact Through the second right and/or left interspace the appropriate stellate ganglion (SG) was exposed A curved, U shaped, metal tube was gently passed around the SG Two pieces of silicone rubber tubing were connected to the metal tube to allow a mixture of ethyl alcohol and propylene glycol at a temperature of −25° C to be circulated The effectiveness of this cold blockade was tested by electrically stimulating the SG through bipolar silver electrodes mounted between the two limbs of the metal tube and connected via a SIU to a Grass S8 stimulator Pulses were usually 5 to 10 V 2 msec duration, and 10 Hz Restitution of normal function was initiated by circulating warm water through the metal tube and assessed by repeating the electrical stimulation

The animal was allowed to stabilize for 1 hour after surgery before starting the study

The arterial blood pressure (BP) (Statham P 23Db), left ventricular pressure, and its derivative (dP/dt) were recorded together with the heart rate (HR) and three ECG leads—D_1, D_2, and V_4—on a Beckman eight channel dynograph The Q T interval was measured since prolongation is associated with an increased possibility of ventricular arrhythmias[10] and the Q T interval is affected by unilateral changes in sympathetic activity [7] It was measured as

$$QT = \frac{Q\,T}{\sqrt{R\,R}}$$

to account for the influence of heart rate [14] Blood gases and arterial pH were kept within the physiological range Body temperature was maintained at 37 5° C

Following stabilization, control HR and BP measurements were recorded Occlusions of the left anterior descending and/or the left circumflex artery were made We counted the number of ectopic beats (premature atrial, nodal, and ventricular beats) during occlusion and for 60 seconds following release The potential significance of various premature ventricular contractions (early PVC s, late PVC s, or PVC's during a run of ventricular tachycardia) was recognized but not investigated in detail Each ectopic beat was assigned the value of 1 for the purposes of analysis The aim of the occlusions was to produce arrhythmias, but the longer the occlusion, the greater the possibility of ventricular fibrillation The occlusions were kept as short as possible The duration of the occlusions of either or both vessels was determined by the occurence of arrhythmias or by reaching 90 seconds of occlusion Once the length of occlusion was established for a given animal, it was maintained for the remainder of the experiment Intervals of 30 minutes between occlusions permitted a return to control conditions Control occlusions were alternated with occlusions performed during stellate ganglion blockade (SGB) Results were considered consistent only if the same qualitative changes were obtained, with CAO of the same duration, for at least two consecutive pairs of trials (control, during SGB, control, during SGB) In three experiments coolers were placed around both SG In two animals vagotomy was performed following the completion of control and SG blockade trials, which were subsequently repeated In two other experiments HR was maintained constant during the blockade trials by atrial pacing In one experiment after consistent results in control and right SGB occlusions, the respirator was turned off in four trials for 30 seconds preceding the CAO

On the basis of the results the experiments were divided into three main groups *Group I*, animals which showed a consistent and reproducible change in the response to CAO during unilateral SGB vs control CAO, *Group II* animals studied with right SGB which showed no such consistent difference between control and right SGB occlusion and *Group III*, animals discarded for one of the following reasons (1) ventricular fibrillation in any of the first to fourth occlusions (2) spontaneous ectopic beats in control periods (3) lack of arrhythmias during a 90 seconds occlusion of both coronary arteries, and (4) damage, by cooling of one SG

Paired and unpaired T tests were used for statistical analysis Figures in the text represent mean ± standard error

Results

In 11 animals (Group I) unilateral SGB during CAO consistently modified arrhythmia production The arrhythmias include atrial, A V nodal, and ventricular premature beats which often resulted in ventricular bigeminy, runs of ventricular tachycardia (five consecutive PVC s), and episopdes of ventricular fibrillation (always fatal) PVC s were present more often than nodal beats however, since no specific pattern was observed they were counted together

In seven animals (Group II) no change was

Fig 2 Tracings, from top to bottom are ECG (D) left ventricular pressure (mm Hg) and its derivative dP/dt (mm Hg/sec.) *A* Effect of electrical stimulation (4 V 2 msec 10 Hz) of the intact left stellate ganglion HR increases from 181 to 214 and the QT interval increased from 0.33 to 0.37 A few seconds after the end of the stimulation this dog had an episode of ventricular tachycardia lasting 20 sec which stopped spontaneously The heart rate increase may depend in part on activation of the right SG which always follows excitation of an intact left SG *B* Control condition HR 200 QT 0 31 C During right SGB HR 1 6 and QT 0 35 *D* 25 sec occlusion of circumflex coronary artery (the first of the experiment) during right SGB Several premature nodal beats preceded a run of ventricular tachycardia This was followed by ventricular fibrillation a few seconds after release

Table II Effects of right and left stellate ganglion blockade (RSGB LSGB) on the occurrence of episodes of ventricular tachycardia (VT) and fibrillation (VF) associated with coronary arterial occlusion

	Episodes	*Experiments*	*Control CAO*	*RSGB CAO*	*LSGB CAO*	*Group I episodes*	*Group II episodes*	*Group III episodes*
VT	14	8	3 (21%)	11 (79%)	0	9	0	5
VF	10	10	2 (20%)	10 (80%)†	0	4	1	5
VT + VF	24	14	5 (21%)	19 (79%)‡	0	13 (54%)	1 (4%)	10 (42%)

*p 0 079
†p 0 005
‡p 0 001

during CAO and right SGB while 21 per cent occurred during control CAO and none during CAO and left SGB The episodes of VF were independent from the order of control and test occlusions and frequently happened at the beginning of the experiment

In four animals CAO s during right SGB were accompanied by changes of the P wave likely to indicate pacemaker shifts and/or by slight shortening of the P R interval These changes never appeared in the other experimental conditions, indicating that a left unilateral increased sympathetic discharge was necessary to produce this effect

Some animals seem to be more prone to arrhythmias than others It is of interest that one

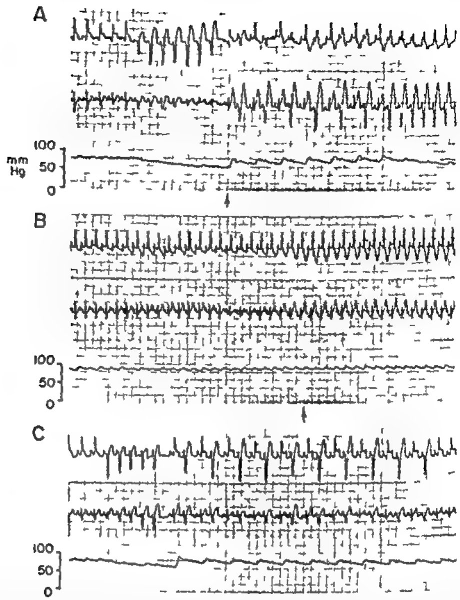

Fig 1 Tracings, from top to bottom are ECG (D and D,) aortic BP Paper speed 25 mm /sec Effect of a 20 sec occlusion of both circumflex and descending coronary artery during the right stellate ganglion blockade (SGB) and in control The arrows indicate the release of the occlusion in C the occlusion was released 2 sec after the end of the strip A CAO during right SGB An episode of VT followed by ventricular bigeminy is evident B CAO in control condition No arrhythmias C CAO during right SCB Again VT and ventricular arrhythmias These occlusions were consecutive and they are trials 2 3 and 4 of experiment 6 (Table I) The control occlusions preceding A and following C produced only a few ectopic beats

experiments were 136 ± 9 mm Hg and 181 ± 7 b p m

1 Effect of right SGB during CAO In eight experiments (52 trials) CAO s during right SGB were consistently and reproducibly associated with more cardiac arrhythmias than control occlusions (Fig 1 and Table I)

In Fig 1 two occlusions of both circumflex and left anterior descending coronary arteries for 20 seconds (*A* and *C*) led to ventricular tachycardia followed by ventricular bigeminy while three similar control occlusions (one shown in *B*) performed alternatively with those during right SGB had no associated arrhythmias

Two animals had intact vagi initially Subsequent vagotomy did not modify the responses, i e, CAO's during right SGB continued to have more arrhythmias than control occlusions In two experiments heart rate was maintained constant by atrial pacing and still more ectopic beats were present during CAO and right SGB

Heart rate at the end of CAO during right SGB was 158 ± 6 compared to 175 ± 7 b p m at the end of control CAO

The occurrence of ventricular tachycardia (VT) and fibrillation (VF) was related to the conditions during which CAO was performed (Table II) 79 per cent of these episodes occurred

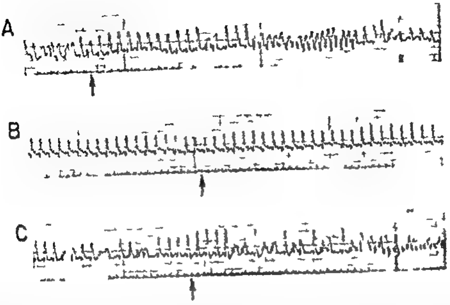

Fig 4 Effect of a 90 sec occlusion of the circumflex coronary artery in an animal having the descending coronary artery ligated at the beginning of the experiment in control condition and during left stellate ganglion blockade (SGB) A CAO in control condition Episodes of VT before and after release of the occlusion with several PVC s B CAO during left SGB No arrhythmias C CAO in control condition There are several PVC s which are followed by VT which a few seconds later precipitates in ventricular fibrillation A B and C are consecutive trials. The asterisks indicate ectopic beats

dog which had an episode of VT during the first CAO associated with right SGB and died in VF a few seconds after release had earlier shown VT following brief stimulation of the left SG (Fig 2) In both situations the heart of this animal was receiving a unilateral sympathetic discharge through the left SG

3 *Effect of left SGB during CAO* In three animals in which arrhythmias were absent during control CAO and appeared during CAO and right SGB left SGB did not produce any arrhythmia Therefore the effect of left SGB was tested only in animals responding with consistent arrhythmias to CAO this explains the difference between control CAO in Tables I and III In three experiments in which the control occlusions consistently produced arrhythmias left SGB always suppressed or greatly reduced them (Figs 3 and 4 Table III)

As shown in Fig 4 while the control occlusion of the circumflex for 90 seconds in an animal with previous ligature of the left descending led to episodes of VT and eventually to VF the occlusions during left SGB were uneventful showing an important protective effect

No episodes of VT or VF occurred during CAO s associated with left SGB While episodes of alternation of the T wave (alternation of two configurations of the T wave without any concomitant change in the QRS complex) occurred occasionally during control CAO s (Fig 3 A) and during CAO s with right SGB they were never observed during CAO and left SGB

Heart rate at the end of CAO during left SGB was 174 ± 11 compared to 180 ± 9 b p m at the end of control CAO

C Results in Group II animals The control values of BP and HR in these seven experiments were 139 ± 6 mm Hg and 152 ± 4 b p m

Almost no difference was present in the arrhythmias associated with control CAO compared to CAO during right SGB when there were differences these were usually minor and inconsistent i e never reproducible for at least two pairs of consecutive trials Left SGB was not studied The type of CAO was the same as in Group I and often when no arrhythmias appeared the occlusions were maintained for longer periods of time

In these animals arrhythmias were elicited in a very irregular and erratic way, at variance with Group I animals where for a given occlusion in control or during SGB the number of ectopic beats was fairly constant and reproducible

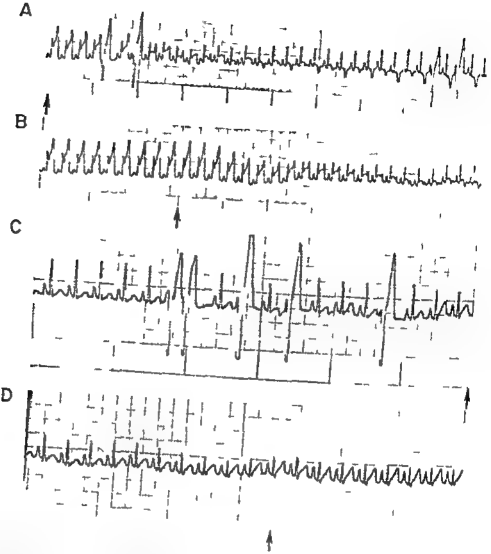

Fig 3 Effect of occlusion of both circumflex and descending coronary arteries in control condition and during left stellate ganglion blockade (SCG) *A* 45 sec CAO in control condition At release (arrow) there are four PVC s and alternation of the T wave *B* 45 sec CAO during left SGB The ischemic changes are evident as in *A* but there are no arrhythmias nor T wave alternation *C* 15 sec CAO in control condition Five PVC s precede the release *D* 15 sec CAO during left SGB No arrhythmias All of these trials were consecutive

Table III Effect of left stellate ganglion blockade (LSGB) on the number of ectopic beats associated with coronary arterial occlusion

Exp No	Trials	Coronary artery occluded (sec)	Control coronary artery occlusions					LSGB coronary artery occlusions				
			Blood pressure†	Heart rate†	Ectopic beats: During	After‡	Total	Blood pressure†	Heart rate†	Ectopic beats: During	After‡	Total
1	1 2	Circ (30)	100 100	158 165	14	0	14	90 85	140 144	0	0	0
	3 4	Circ (30)	115 115	132 144	12	0	12	90 8[illegible]	140 144	0	0	0
2	1 2	Circ + desc (45)	170 155	182 189	[illegible]	4	4	170 1[illegible]	16[illegible] 174	0	0	0
	3 4	Circ + desc (45)	170-165	174 174	5	0	5	170 170	180 180	0	0	0
3	1 2	Circ (90)§	105 90	192 202	23	17	40	100 9[illegible]	192 200	4	4	8
	3 4	Circ (90)§	110-105	195 204	9	26	3[illegible]	100 90	195 204	4	6	10

Change from control significant $p < 0.05$

†Values at beginning and end of occlusion

‡ After" is the [illegible] sec immediately following release of occlusion

§One hour after ligature of the left anterior descending coronary artery

location have been described following the stimulation of left SG and did not occur during stimulation of right SG[20]

Rationale for identifying two groups of animals Seven animals (Group II) did not show any change in the number of arrhythmias after blockade of the right stellate ganglion Detailed examination of the data from these seven animals revealed several differences between them and the animals which showed more arrhythmias following right SG

While BPs were similar (Group I 136 ± 9 Group II 139 ± 6 mm Hg) the HRs were significantly ($p < 0.005$) different (Group I 181 ± 7 Group II 152 ± 4 b p m) In vagotomized animals a higher HR when BP is similar is likely to indicate higher sympathetic activity higher level of circulating catecholamines or a greater sensitivity of the sinus node to catecholamines Since our experiments were based upon the effects of withdrawing the resting level of sympathetic activity it is evident that if this level was low no change could be expected by its removal

Right SGB was less effective in reducing HR in these animals They contributed to only 4 per cent of the total number of episodes of VT or VF It is of interest that the animals belonging to Group III which had episodes of VT or VF (42 per cent of the total) had BPs and HRs similar to Group I animals (130 ± 5 mm Hg and 172 ± 9 b p m)

These differences suggest that sympathetic activity was less in Group II than Group I In addition Group II animals seemed to be less reactive to CAO in terms of arrhythmia production.

Role of the vagi heart rate and site of myocardial ischemia

A Vagotomized dogs were used because by eliminating the tonic inhibition mediated by cardiopulmonary vagal afferents the sympathetic activity is higher In addition vagotomy unmasks the fall in HR during right SGB and prevents possible reflex changes involving afferent or efferent vagal components[3, 22] In two dogs however the vagi were cut during the experiment (see Table I) without modifying the effect of right SGB indicating that in our experimental conditions the afferent and efferent components of the vagi were not essential

B It has been suggested that the antiarrhythmic effect of cardiac sympathetic denervation depends mainly upon a reduction in heart rate[23] This is understandable because changes in heart rate influence the metabolic requirements of the heart and the rate at which ischemia develops In our experiments however the protective effect of left SGB was associated with a minor reduction in heart rate (174 ± 11 at the end of CAO during left SGB versus 180 ± 9 b p m at the end of control CAO) (Table III) moreover the reduction in heart rate resulting from right SG blockade did not prevent the development of arrhythmias Bradycardia has been demonstrated to increase temporal dispersion of refractory period duration and to facilitate ectopic beat formation[25] This is generally valid however for heart rates lower than 90 b p m[26] In our experiments right SGB was accompanied by a reduction in HR but not by bradycardia in fact HR during right SGB and CAO was 164 ± 19 b p m and never in the vagotomized dogs lower than 130 b p m which does not seem enough to justify increased arrhythmias In two experiments HR was held constant by atrial pacing and still more arrhythmias associated with CAO during right SGB were observed Therefore it seems that the effects of unilateral SGB on the production of arrhythmias associated in our experiments with CAO were independent of the limited changes observed in heart rate

C Right and left SGB produced their effect during occlusions of the circumflex left descending or both coronary arteries (Tables I and III) It seems therefore that the site of myocardial ischemia did not influence qualitatively the results

D The opposite effect on arrhythmia production of right vs. left SGB rules out the possibility that the direction of the observed change was predetermined or influenced by some unknown variable and leaves the unilateral change in cardiac sympathetic activity as the one responsible factor Presently we have no explanation for our findings although one may speculate that the differences in the anatomical distribution of right and left sympathetic nerves play a role

Role of afferent and efferent sympathetic activity Cooling interrupts afferent as well as efferent sympathetic activity The increase in efferent sympathetic activity during CAO often results from a cardio cardiac reflex[2] initiated by excitation of afferent sympathetic fibers having their sensory endings in the heart [28] The section

Only one (4 per cent) out of the total number of 24 episodes of VT or VF happened in Group II experiments (Table II)

The mean reduction in HR produced by right SGB was 30 per cent less than that obtained in Group I experiments

D Results in Group III animals Seven experiments were discarded from this study because of ventricular fibrillation during one of the first occlusions (five dogs) or because of spontaneous arrhythmias (two dogs) The control values of BP and HR were 130 ± 5 mm Hg and 172 ± 9 b p m These animals contributed to 42 per cent of the episodes of VT or VF (Table II)

Four experiments were discarded because of the total lack of arrhythmias also with long CAO s and even after permanent ligature of the left descending coronary artery The control values of BP and HR were 124 ± 8 mm Hg and 155 ± 11 b p m

Four experiments were discarded because of irreversible damage of the right SG during the first or second cooling The control values of BP and HR were 126 ± 12 mm Hg and 156 ± 3 b p m

Discussion

The main conclusion of this paper is that blockade of the right stellate ganglion during coronary arterial occlusion increased arrhythmias whereas blockade of the left SG had opposite results Thus the effect of the right SG blockade could not be predicted from the results obtained using bilateral stellectomy [4]

The arrhythmogenic effect of right SG blockade is supported by the following data (1) ventricular fibrillation threshold (VFT) which is known to be increased by bilateral stellectomy [1] is also increased by ablation of the left SG but is reduced by ablation of the right SG [16] Since CAO also reduces VFT [16,17] it would be anticipated that the combination of CAO and right SGB would produce more episodes of VF and in fact 80 per cent of VF episodes occurred under these circumstances (Table II) (2) In unanesthetized dogs ablation of the right SG favored the appearance during CAO or submaximal exercise of several arrhythmias which were absent in the intact animals and disappeared after bilateral stellectomy [18] Therefore the effects of right SGB as obtained in acute experiments are reproducible also in conscious animals

The technique of reversible blockade of the stellate ganglia which allows observation of arrhythmias associated with CAO during SGB and thereafter in control condition several times in the same animal, rules out the possibility that changes in animal condition might have been the determinants of the differences observed

Effects of unilateral blockade of stellate ganglia during brief coronary artery occlusions In the present experiments major arrhythmias, such as ventricular tachycardia (VT) or fibrillation (VF), which occurred during brief (< 90 seconds) coronary arterial occlusions, required the presence of an intact left SG It has been reported that arrhythmias are produced with or without CAO, by electrical stimulation of the left cardiac sympathetic nerves [11, 12, 19] while it seems that stimulation of the right SG is not arrhythmogenic [11] Excitation of sympathetic activity by CAO, in the presence of a right SGB leads to a unilateral discharge through the left SG and therefore our experimental condition may be comparable to electrical stimulation of the left SG Our data are consistent with previous experiments involving electrical stimulation and show how neurally mediated arrhythmias are mainly dependent upon the left SG This is further confirmed by two other observations (1) arrhythmias during CAO have been abolished by section of the ventral roots C8 to T5, which represent the main sympathetic outflow to the heart on the *left* side only, while the right ventral roots were intact (unpublished) and (2) arrhythmias produced by central nervous system stimulation during myocardial ischemia are reduced or suppressed by ablation of the left SG (Dormer, K , Schwartz P J and Stone H L Work in progress)

Alternation of the T wave with CAO occurred in control occlusions and in occlusions during right SGB hence it also required the presence of an intact left SG This confirms previous experiments in which alternation of the T wave was produced by stimulation of left SG [8] This phenomenon often follows abrupt increases in sympathetic activity in patients with the long Q T syndrome [8] in whom activity in the right SG is likely to be reduced and precedes ventricular fibrillation Changes in the P wave suggesting shifts in the location of the pacemaker occurred only during CAO associated with right SGB, i e during unilateral increased activity through the left SG It is noteworthy that shifts in pacemaker

and Brown, A. M. A cardio-cardiac sympathovagal reflex in the cat, Circ. Res. 32 215 1973
Hope, R. R., Williams, D O El Sherif N Lazzara R and Scherlag, B J The efficacy of antiarrhythmic agents during acute myocardial ischemia and the role of heart rate, Circulation 50 507 1974
Han, J Detragha, J., Millet D and Moe G Incidence of ectopic beats as a function of a basic rate in the ventricle, Am. Heart J 72 632, 1966
Han J Millet, D Chizzonitti, B and Moe G Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate Am Heart J 71 481 1966
Chadda, K. D Banka V S and Helfant R H Rate dependent ventricular ectopia following acute coronary occlusion, Circulation 49 654 1974
27 Brown, A. M., and Malliani, A. Spinal sympathetic reflexes initiated by coronary receptors, J Physiol. 212 685, 1971
28. Malliani, A. Recordati, G., and Schwartz, P J Nervous activity of afferent cardiac sympathetic fibres with atrial and ventricular endings, J Physiol. 229 457 1973
29 Schwartz, P J., Foreman, R. D., Stone H L., and Brown, A. M. Arrhythmias depending upon a cardio-cardiac sympathetic reflex, Fed. Proc. 34 421 1975
30. Lown, B and Wolf M A. Approaches to sudden death from coronary heart disease Circulation 44 130 1971

of the dorsal roots which contains these sympathetic afferent fibers reduces the arrhythmias produced by CAO [9] The interruption of the afferent limb of an excitatory reflex might have contributed to part of the effect of left SGB

Conclusion

Right and left stellate ganglion blockades have opposite effects on the genesis of arrhythmias associated with coronary artery occlusions

Further investigations are necessary to elucidate the basic mechanisms underlying the facts that we have shown to occur The arrhythmogenic effects of right SGB during CAO and the antiarrhythmogenic effects of left SGB suggest, however, that the two stellate ganglia may have different effects upon cardiac excitability

The protective effect of left SG blockade may be of clinical interest in situations like the early phase of myocardial infarction, characterized by high incidence of PVC s and ventricular fibrillation [30]

Summary

In anesthetized dogs the circumflex and/or the anterior descending coronary artery were briefly occluded (10 to 90 seconds) and ectopic beats occurring during the occlusion or for 60 seconds following release were counted Control occlusions were alternated with occlusions performed during complete reversible unilateral blockade of either the right or the left stellate ganglion This was achieved with thermodes through which coolant was circulated In this way the shortcomings associated with stellectomy which is irreversible, are avoided Blockade of the right stellate ganglion increased the number of ectopic beats associated with coronary occlusion The occurrence of episodes of ventricular tachycardia and fibrillation was also greater By contrast blockade of the left stellate ganglion reduced or abolished occlusion induced arrhythmias These effects are independent of changes in heart rate or vagal activity, they depend solely upon unilateral alteration in sympathetic tone and are not demonstrable when such tone is low We suggest that the right and left cardiac sympathetic nerves have a different influence upon cardiac excitability

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REFERENCES

1 Peterson D F Kaspar R L and Bishop V S Reflex tachycardia due to temporary coronary occlusion in the conscious dog Circ. Res. 32 652 1973.
2. Malliani, A Schwartz, P J and Zanchetti, A. A sympathetic reflex elicited by experimental coronary occlusion Am J Physiol 217 703 1969
3. Costantin L. Extracardiac factors contributing to hypotension during coronary occlusion Am J Cardiol 11 205 1963
4 Harris A. S Estandia A and Tillotson R. F Ventricular ectopic rhythms and ventricular fibrillation following cardiac sympathectomy and coronary occlusion, Am J Physiol 196 505 1951
5 Schwartz P J Periti M and Malliani A The long Q T syndrome AM HEART J 89 378, 1975
6. Randall W C and Rohse W G The augmentor action of the sympathetic cardiac nerves, Circ. Res. 4 470, 1956
7 Yanowitz, F Preston J B and Abildskov J A Functional distribution of right and left stellate innervation to the ventricles Production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone Circ Res. 18 416 1966.
8. Schwartz P J and Malliani A Electrical alternation of the T wave Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q T syndrome AM HEART J 89 45, 1975
9 Han J and Moe G K Nonuniform recovery of excitability in ventricular muscle Circ Res. 14 44 1964
10 Han J and Goel B G Electrophysiologic precursors of ventricular tachyarrhythmias Arch Intern. Med. 129 749 1972
11 Armour J A Hageman G R and Randall, W C. Arrhythmias induced by local cardiac nerve stimulation, Am J Physiol 223 1068 1972
12 Hageman G R Goldberg J M Armour J A and Randall W C Cardiac dysrhythmias induced by autonomic nerve stimulation Am J Cardiol. 32 823, 1973
13 Denn M J and Stone H L Innervation of coronary arteries (abst) Physiologist 17 208 1974
14 Bazett H C An analysis of the time relations of the electrocardiograms, Heart 7 353 1920
15 Kliks B R Burgess M J and Abildskov J A The influence of sympathetic tone on ventricular fibrillation threshold during experimental coronary occlusion (abst) Circulation 46 115 1972
16 Schwartz, P J Snebold N G and Brown A M Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold (abst.) Am J Cardiol 35 169 1975
17 Han J Ventricular vulnerability during acute coronary occlusion Am J Cardiol 24 857 1969
18 Schwartz P J and Stone H L Role of right stellate ganglion during exercise (abst) Submitted for publication
19 Harris A S Otero H and Bocage A J The induction of arrhythmias by sympathetic activity before and after occlusion of a coronary artery in the canine heart, J Electrocardiol 4 34 1971
20 Geesbreght, J M and Randall W C Area localization of shifting cardiac pacemakers during sympathetic stimulation Am J Physiol 220 1522 1971
21 Guazzi M Libretti A and Zanchetti A Tonic reflex regulation of the cat blood pressure through vagal afferents from the cardiopulmonary region Circ. Res. 11 7 1962
22 Schwartz P J Pagani M Lombardi F Malliani, A

them A left thoracotomy was performed in all dogs and the heart suspended in a pericardial cradle. The circumflex branch and the anterior descending branch (LAD) of the left coronary artery (about 2 cm distal from the origin) were exposed by blunt dissection In 13 dogs with chronic coronary occlusions a wide bore bent metal cannula was inserted into the aorta via the left subclavian artery and connected to a silicone rubber tube of 3 mm inner diameter The left circumflex branch distal to the Ameroid constric tor was cannulated with a second metal cannula of the same diameter and connected to the sili cone rubber tube This aortocoronary bypass could be opened and closed by clamping the tube Peripheral coronary pressure was measured in the circumflex artery via Statham pressure trans ducer Bypass flow was measured by a cannu lating flowmeter (Statham) inserted in the tube A P.E catheter was introduced into the left atrium via the left atrial appendage for measure ment of left atrial pressure This catheter was also used for injection of tracer microspheres Finally the aorta distal to the left subclavian artery as well as the brachiocephalic artery were prepared and equipped with tourniquets

Tracer microspheres (TM) Regional myocar dial blood flow was measured with the TM technique Six different isotopes were used I 125 Ce-141 Cr 51 Sr 85 Nb 95 and Sc 46 I 125- and Nb-95-labeled beads had a diameter of 15 μ the others were 8 to 10 μ. To avoid TM aggregation benzalkonium 0 05 per cent and heparin were added to the suspension and ultrasound deaggre gation was performed with a Branson B 12 Sonifier before every injection Approximately two million beads were injected for every blood flow determination The TM data (counts per minute per milligram of tissue) were calibrated to milliliters per minute × 100 Gm of tissue by the reference sample method of Buckberg and asso ciates Domenech and associates and Utley and associates.[12] For this purpose a wide bore catheter was placed into the terminal aorta via the femoral artery and connected to a Gilford constant speed withdrawal pump at 22 ml per minute After the experiment the animals were killed by an overdose of sodium pentobarbital The heart was removed and fixed in phosphate buffered 4 per cent formaldehyde for [illegible] days The hearts were totally cut into approximately 400 tissue pieces of known anatomical localization Each sample was accurately weighed coded and transferred to a disposable plastic test tube The tubes were automatically transported by a Selec tronic sample changer into and out of a 3 inch Na I well type scintillation crystal The transport was controlled by a ND 812 8 K 12 bit process computer The compound gamma ray spectrum of the six radionuclides present in the tissue samples was analyzed by the ND 812 process computer Background correction and spillover produced by the Compton scattering were taken into account Details of the computer program have been published elsewhere Corrected activ ities were expressed as counts per minute per milligram The data were printed out on a tele type printer and punched in parallel on paper tape The paper tape was fed into an IBM 130 computer for graphic presentation via Calcomp plotter Statistical significance was accepted at the 5 per cent probability level when using Student s t test (for paired and unpaired data)

Design of the experiment The first TM injec tion was made after a control period of approxi mately 15 min when all hemodynamic variables had stabilized Arterial and coronary sinus blood was withdrawn simultaneously and oxygen content determined Aortic pressure left ventric ular pressure left atrial pressure left ventricular dp/dt peripheral coronary pressure bypass flow and ECG Lead II were recorded continuously In dogs with chronic coronary artery occlusions and bypass TM injections were made during open and closed bypass Thereafter the aorta was cross clamped for registration of isovolumetric contrac tions Mitral insufficiency could be excluded by comparison of the pressure tracings of the left atrium and the left ventricle Cross clamping of the aorta was released when mean left atrial pressure reached 20 mm Hg Norepinephrine 2 μg per minute per kilogram of body weight was infused after both nervi vagi had been cut After stabilization of all hemodynamic variables other TM injections were given in dogs with chronic coronary artery occlusions with open and there after with closed bypass Isovolumetric pressures were registered after cross clamping of the aorta Under ongoing norepinephrine infusion coronary dilatory reserve was tested by injection of TM at peak reactive hyperemia after 20 seconds of occlu sion of the LAD or the LC artery in normal dogs and the LAD artery alone in dogs with chronic coronary artery occlusions Finally a coronary

Vascular and cardiac contractile reserve in the dog heart with chronic multiple coronary occlusions

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The relation of coronary collaterals to cardiac function is still a matter of dispute[1-5] In recent reports from this laboratory[6,7] we have shown that the development of a collateral circulation after multiple chronic coronary artery occlusions protects the myocardium against infarction This was possible only when the progression of arterial stenosis was sufficiently slow to allow the collaterals to develop However, hemodynamic changes can produce ischemia in these hearts in the early stage of collateralization[7] Therefore we were interested in the functional capacity of the collateralized heart In this study we evaluated the contractility reserve in the dog heart 2 weeks after chronic coronary artery occlusion without infarction It was anticipated that with the aortocoronary bypass preparation the normal myocardial perfusion would be restored, thereby allowing comparison of the collateralized heart with the normal situation

Methods

The experiments were carried out in 34 mongrel dogs of either sex, of unknown age with an average body weight of 21 kilograms The dogs were divided into three groups (A) a control group of 15 normal dogs, (B) a group of 19 dogs which were studied 4 weeks after implantation of two Ameroid constrictors on the coronary arteries (C) in 13 of these dogs the occluded circumflex branch of the left coronary artery was bypassed (aortocoronary bypass)

Surgical procedures Thirty dogs were operated on under sterile conditions during anesthesia with piritramide,[8] 2 5 mg per kilogram subcutaneously, and sodium pentobarbital 15 mg per kilogram intravenously Artificial respiration was maintained with a Bird Mark 7 during thoracotomy which was performed through the fourth left intercostal space The heart was suspended in a pericardial cradle while Ameroid constrictors of appropriate size were slipped over the circumflex branch of the left coronary artery (LC) and the right coronary artery close to their respective origins The chest was closed in layers and the dogs were allowed to recover

Experimental procedures All animals were anesthetized with piritramide, 5 mg per kilogram subcutaneously, and sodium pentobarbital, 10 mg per kilogram intravenously Anesthesia was maintained with 80 per cent and 20 per cent nitrous oxide-oxygen under intermittent positive pressure respiration with a Bird Mark 7-Mark 4 combination Aortic blood pressure was measured via a 7 Fr catheter (femoral artery) connected to a Statham pressure transducer Left ventricular pressure and its time derivative (dp/dt) were measured with a 5 Fr Millar type catheter tip manometer (left carotid artery) and an active RC circuit A 8 Fr Goodale Lubin catheter was advanced via the jugular vein into the coronary sinus under fluoroscopic guidance for coronary sinus sampling A Cordis pigtail catheter was placed into the left ventricle via the right brachial artery for measuring left ventricular end diastolic pressure Both nervi vagi were prepared in the neck and loose ligatures were placed around

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Table I Experimental data after cross clamping of the aorta (mean value ± S E M) and comparison of the control conditions with the norepinephrine conditions in the three groups*

	HR (min)	IP (mm Hg)	dp/dt max (mm Hg/sec)	dp/dt min (mm Hg/sec)	MLAP (mm Hg)
Control					
Normal dogs (Group A)	133 ± 8	203 ± 5	[illegible]530 ± 9[illegible]	19[illegible] ± 109	5 9 ± 0 1
Dogs with CCO BPC (Group B)	135 ± 5	217 ± 8	2,880 ± 343	1 920 ± 233	6 0 ± 0 7
Dogs with CCO-BPO (Group C)	134 ± 6	219 ± 13	3 040 ± 411	2,3 0 ± 480	6 0 ± 0 7
Norepinephrine					
Normal dogs (Group A)	[illegible]21 ± 5	326 ± 16	10 [illegible]0 ± [illegible]80	51 [illegible] ± 60[illegible]	6 38 ± 0 7
Dogs with CCO BPC (Group B)	221 ± 9	32[illegible] ± 10	10 914 ± 9[illegible]2	5,200 ± 598	6 0 ± 1 4
Dogs with CCO BPO (Group C)	222 ± 9	331 ± 9	11 3 0 ± 10[illegible]	5 3[illegible]1 ± [illegible]08	6 0 ± 1 4

Abbreviations BPC aortocoronary bypass closed BPO aortocoronary bypass opened CCO chronic coronary artery occlusion dp/dt max peak value of the time derivative of the left ventricular pressure dp/dt min peak negative value of the time derivative of the left ventricular pressure HR, heart rate IP isovolumetric left ventricular systolic pressure MLAP mean left atrial pressure.

between groups (see Table II) Similarly the mean values for aortic pressure heart rate and dp/dt max for the three groups were not significantly different The ratio of diastolic peripheral coronary pressure to aortic pressure in Group B was 0 32 whereas with open bypass (Group C) the ratio of diastolic pressure in the LC to that in the aorta was 0 98 and not significantly different from unity

C Regional myocardial blood flow under norepinephrine infusion During infusion of norepinephrine subendocardial blood flow in normal dogs increased homogeneously from 68 to 323 ml per minute × 100 Gm in the LAD area and from 65 to 360 in the LC area The subepicardial flow increased from 65 to 224 ml per minute × 100 Gm and from 62 to 226 ml per minute × 100 Gm in the respective areas (Fig 3)

In dogs with chronic coronary artery occlusions myocardial blood flow was nonhomogeneous (Fig 3) The flow to the subendocardium supplied by the LAD increased from 76 to 530 ml per minute × 100 Gm The latter value is significantly higher than the respective value in normal dogs The epicardial flow during norepinephrine administration was 291 ml per minute × 100 Gm not significantly different from normal dogs The myocardium supplied only by collaterals received less blood in dogs with chronic coronary artery occlusions than the area supplied by the LC in normal dogs The difference was statistically significant only for the endocardium and not for the epicardium

In dogs with chronic coronary artery occlusions and coronary bypass myocardial blood flow was again homogeneously distributed The subendocardial layers received more blood than the subepicardial layers in the area supplied by the LAD artery as well as in the area supplied by the aortocoronary bypass Comparing the situation before and after bypass in dogs with chronic coronary artery occlusions the flow to the subendocardium in the area supplied by the LAD decreases significantly while epicardial flow is unchanged In the LC area the subendocardial flow increases significantly after bypass and the epicardial flow is unchanged After aortocoronary bypass (Group C) the myocardial blood flow to the LAD and LC area is not significantly different from that of normal dogs (Table II)

The mean values for the myocardial oxygen consumption (Table II) were determined only in normal dogs and in dogs with CCO plus aortocoronary bypass These values showed no significant differences between these groups The small absolute differences between groups for heart rate mean aortic pressure and dp/dt max were not significant

D Regional myocardial blood flow during maximal vasodilation plus norepinephrine In normal dogs the coronary dilatory reserve of the subendocardial layers and the subepicardial layers was not different ($p > 0.05$ for sets of paired observations) There was no significant difference in coronary reserve between the LAD and the LC areas In dogs with chronic coronary artery occlusions myocardial blood flow is nonhomogeneously distributed

In comparison with normal dogs myocardial blood flow during maximal dilation in dogs with chronic coronary artery occlusions was not different in the area supplied by the LAD artery

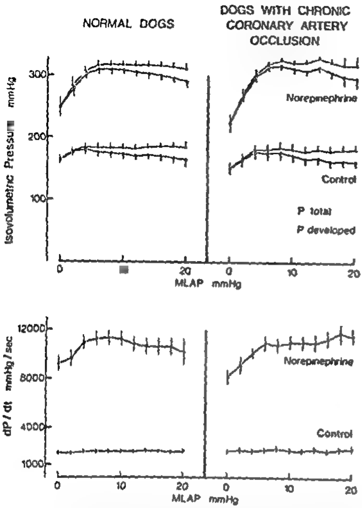

Fig 1 The mean values of the peak left ventricular systolic pressure and the peak left ventricular dp/dt max after cross clamping of the aorta are shown for normal dogs and for dogs with chronic coronary artery occlusions It is evident that total pressure increases with raising mean left atrial pressure (MLAP) until a plateau is reached (between 4 and 6 mm Hg) Developed pressure has its peak at 6 mm Hg and then declines gradually Dp/dt max under control conditions shows no change with increasing left atrial pressure After norepinephrine an increase of dp/dt max at low left atrial pressures is noted with higher atrial pressures no further changes occur

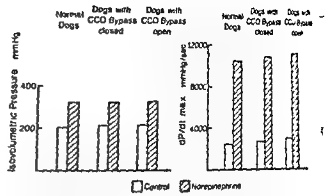

Fig 2 Contractility and contractility reserve in normal dogs and dogs with chronic coronary artery occlusions (CCO) with closed and open aortocoronary bypass are presented. Neither under control conditions nor under norepinephrine does a significant difference ($p > 0.05$) exist between groups.

angiogram was made with the Sones technique to document complete closure of both arteries by Ameroid constrictors Thereafter the LAD was opacified and the collaterals to the left circumflex and the right coronary artery were demonstrated

Results

A Contractility and contractility reserve Under control conditions, cross clamping of the aorta resulted in the stabilization of isovolumetric peak left ventricular pressure (I P) over the range of 4 to 20 mm Hg of left atrial pressure (LAP) as shown in Fig 1 The calculated regression slopes of values for total isovolumetric pressure developed isovolumetric pressure, and left ventricular dp/dt were not significantly different from zero over the range of 4 to 20 mm Hg LAP (Fig 1) Total I P, measured at 6 mm Hg LAP, was 203 mm Hg for normal dogs (Group A) 214 mm Hg for dogs with chronic coronary artery occlusions (Group B), and 219 mm Hg for dogs with chronic coronary artery occlusions plus bypass (Group C) (Fig 2 Table I) These values were not significantly different from one another Similarly, no significant difference was noted among the three groups with regard to values of dp/dt max and dp/dt min (Fig 2, Table I)

After infusion of norepinephrine I P reached a plateau at 4 mm Hg LAP (Fig 1) The calculated regression slopes for total and developed I P and dp/dt max were not significantly different from zero over the range of 4 to 20 mm Hg LAP No significant difference could be detected among the three groups in terms of magnitude of increase from control of total I P as measured at 6 mm Hg LAP, max dp/dt or heart rate The absolute magnitudes of increase of these variables expressed as times initial control for Groups A B and C respectively were 1 61, 1 50, and 1 51 for total I P 4 17 3 79 and 3 74 for max dp/dt, and 1 66 1 64 and 1 66 times initial control for the heart rate

B Regional myocardial blood flow in control conditions The regional myocardial blood flow pattern was homogeneous in every group (see Table II) There was no difference between groups regarding blood flow to the respective myocardial areas while the endo/epi ratio was not different from unity in all groups There was no difference in myocardial oxygen consumption

HR (min.)	AOP_m (mm. Hg)	LV dp/dt max (mm Hg/sec)	AVDo (vol %)	MVo (mL/min × 100 mg)	PCPd/AOPd
109	89	2, 00	11 7	7.8	—
± 8.8	± 8 8	± 204	± 1 5	± 1 4	
10/	93	2 630	11.5	7 9	0 32
– 6.11	± 8 6	± 3?0	± 1 14	± 1 39	± 0 04
10/	87	2,6 0	10 6	6.4	0 98
10 6	± 10 2	± 304	± 1 44	± 1 27	± 0 02
222	149	7 380	13 0	30 1	—
– 7.3	± 8 3	± 66	± 1.55	± 3 67	
220	149	8 1 0	10 4	—	0 33
5 6	± 6 4	± /03	± 1 6		± 0 03
?19	149	9 100	8.8	31 7	0 97
– 4 6	± 10 9	± 6 8	± 0 4	± 5 3	± 0 02
??1	145	7 133	—	—	—
– 7.2	± 5 3	± 9 6			
236	147	6,?00	—	—	—
± 7 6	± 6 3	± 1 1 0			
22?	149	6 300	—	—	—
– 9 5	± 13 2	± 1 1?9			

tion Under control conditions they found a small increase in dp/dt max over a wide range of left ventricular volumes Schaper and associates could demonstrate that dp/dt max is afterload independent Ross and associates[9] also showed that dp/dt max was unaltered during isovolumet ric high afterloaded and unloaded contractions

Concerning peak isovolumetric pressure we found a steady increase in control conditions as well as under norepinephrine up to 4 to 8 mm Hg of left atrial pressure at which point a plateau was reached (Fig 1) When developed pressure was calculated a maximum was reached at 6 mm Hg atrial pressure followed by a small decrease of peak pressure with increasing atrial pressures In the isolated heart Monroe and associates found a similar curve for developed pressure although their curve peaked at 30 mm Hg During control conditions peak isovolumetric pressures in our study were 203 mm Hg for normal dogs and 217 mm Hg in dogs with chronic coronary occlusions Kumar and associates[2] found in the intact unanesthetized dog a developed pressure of 215 mm Hg with an end diastolic pressure of 20 mm Hg. Monroe and associates[21] found in the isolated

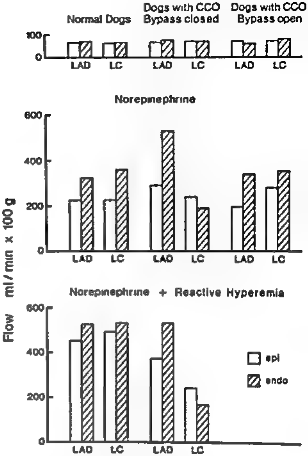

Fig 3 The myocardial blood flow distribution of the left ventricle is shown under control conditions (upper panel) during norepinephrine infusion and during norepinephrine infusion plus reactive hyperemia The left ventricle is divided into the area supplied by the left anterior descending branch (LAD) and into the area supplied by the left circumflex branch of the left coronary artery (LC) Both areas are further divided into a subepicardial (*epi*) and a subendocardial (*endo*) part In dogs with chronic coronary occlusions (CCO) the LC area is perfused selectively by collaterals. After the aortocor onary bypass has been opened the LC area receives blood only through the bypass

heart with an intact pericardium an average systolic pressure of 197 mm Hg at 20 mm Hg end diastolic pressure

The fact that myocardial blood flow under control conditions in dogs with chronic coronary artery occlusions is homogeneously distributed is due to an adequate development of collateral vessels[7] However previous reports from this laboratory have demonstrated that the coronary reserve in these hearts is severely diminished 2 weeks after complete coronary occlusion During

Table II Experimental data obtained in the three groups (mean values ± S E M) comparing contrc conditions, norepinephrine, and norepinephrine plus reactive hyperemia*

	LAD flow (ml /min × 100 Gm)				*LC or collateral flou (mL/min × 100 Gm.)*			
	Total	*Endo*	*Epi*	*Endo/epi*	*Total*	*Endo*	*Epi*	*Endo/e*
Control								
Normal dogs	6b	68	65	1 07	64	65	6?	[illegible]
(Group A)	± 4 9	± 6 7	± 4 2	± 0 10	± 3 2	± 5 3	± 2 1	[illegible]
Dogs with CCO	70	76	65	1 14	66	70	68	[illegible]
BPC (Group B)	± 14 3	± 19 6	± 10 6	± 0 2	± 15 1	± 20	± 14 7	[illegible]
Dogs with CCO	64	60	72	0 89	77	79	/3	[illegible]
BPO (Group C)	± 12 6	± 11 8	± 15 9	± 0 12	± 17 6	± 16 3	± 16 3	[illegible]
Norepinephrine								
Normal dogs	268	323	224	1 48	277	360	2?6	[illegible]
(Group A)	± 26 3	± 32 7	± 25 3	± 0 1	± 35 0	± 35 0	± 6 3	[illegible]
Dogs with CCO	401	530	291	1 87	213	189	240	[illegible]
BPC (Group B)	± 47 0	± 66 0	± 35 6	± 0 18	± 19 5	± 21 9	± ?0 3	[illegible]
Dogs with CCO	259	339	196	1 65	312	355	283	[illegible]
BPO (Group C)	± 37 0	± 46 8	± 30 0	± 0 17	± 39 3	± 43.6	± 36.7	[illegible]
Norepinephrine + reactive hyperemia								
Normal dogs	501	526	450	1 25	–	–	–	
(Group A)	± 6 39	± 55 9	± 72 2	± 0 12				
Normal dogs	–	–	–	–	531	532	493	[illegible]
(Group A)					± 68 9	± 75 1	± 56 8	[illegible]
Dogs with CCO	452	528	371	1 37	201	165	237	[illegible]
BPC (Group B)	± 93 4	± 119 0	± 66 9	± 0 10	± 52 9	± 55 2	± 52 5	[illegible]

Abbreviations AOP_m mean aortic pressure AVDo mean difference in oxygen content in arterial and coronary sinus blood dp dt max peak value time derivative of the left ventricular pressure Endo blood flow to the endocardial layers Epi, blood flow to the subepicardial layers Endo/epi, ratio of flow to the endocardium and the epicardium HR heart rate LAD blood flow to the area supplied by the anterior descending branch of the [illegible] artery LC blood flow to the area supplied by the circumflex branch of the left coronary artery MLAP mean left atrial pressure MVo oxygen consum of the myocardium PCPd/AOPd ratio of diastolic peripheral coronary artery pressure and diastolic aortic pressure Total total blood flow to the resp area

whereas the blood flow to the collateral dependent area was significantly reduced The subendocardial layers received significantly less blood than the subepicardial layers, as evidenced by an endo/epi ratio of 0 63

The slight differences for heart rate mean aortic pressure and dp/dt max among the groups were again not statistically different

In normal dogs, blood flow to the different compartments during norepinephrine plus reactive hyperemia is significantly higher than during norepinephrine alone (see Table II) In dogs with chronic coronary artery occlusions, myocardial blood flow distribution is not significantly different between norepinephrine plus reactive hyperemia and norepinephrine alone With open bypass, the blood flow during norepinephrine alone is significantly less than in normal dogs during norepinephrine plus reactive hyperemia (Table II)

Discussion

Our results show that contractility and contractility reserve in dogs with two chronically occluded arteries but without infarction is within the normal range With open coronary bypass connection there was also no change in the contractility reserve However some further discussion about the indices for contractility used in this study is needed Left ventricular dp/dt max is a widely accepted index for contractility Several authors found that dp/dt max is influenced by preload[14, 15] and afterload[16, 17] Our results however (see Fig 1), show that dp/dt max under isovolumetric control conditions is almost preload independent With norepinephrine an increase in dp/dt max is seen until 4 to 6 mm Hg left atrial pressure whereas with higher pressures a plateau is reached Fisher and associates[18] found during cardiopulmonary bypass about the same plateau after norepinephrine plus paired stimula

Summary

Nineteen mongrel dogs survived chronic occlusion of the left circumflex and of the right coronary artery without infarction due to the timely development of a collateral circulation Only 38 per cent of the conductance of the arteries before occlusion was restored by collateral vessels In these animals and in 15 control dogs with normal coronary arteries myocardial contractility contractility reserve and myocardial blood flow were studied The same was done in dogs with chronic coronary artery occlusion after aortocoronary bypass Myocardial blood flow was determined with the tracer microsphere technique Contractility reserve was tested and defined as isovolumetric left ventricular pressure and dp/dt max with norepinephrine infusion and cross-clamping of the aorta Contractile reserve was not significantly different between normal dogs and dogs with chronic coronary artery occlusion before and after aortocoronary bypass. Myocardial blood flow during control conditions was homogeneously distributed in all three groups studied The ratio of blood flow to the endocardium and the epicardium was not significantly different from unity Coronary reserve was determined at peak reactive hyperemia following a 20 second period of coronary artery occlusion with ongoing norepinephrine infusion Under these conditions subendocardial flow in normal dogs rose by a factor of 7 9 while subepicardial flow increased 7 4 times In dogs with chronic occlusion of two coronary arteries the increase of myocardial flow was nonhomogeneous subendocardial flow to areas supplied by a normal coronary artery rose by a factor of 7 0 while subepicardial flow increased 5 7 times control Subendocardial collateral flow rose by a factor of 2.4 and subepicardial collateral flow increased 3 5 times control

In normal dogs norepinephrine alone did not result in maximal coronary flow but only 57 per cent thereof Dogs with chronic coronary occlusion however required the entire coronary reserve in areas that were supplied by a normal coronary artery whereas areas supplied by collaterals became ischemic Opening of an aortocoronary bypass restored normal flow to previously ischemic areas and reduced the flow to areas supplied by a normal artery With the bypass open no differences existed between normal dogs and those with two occluded coronary arteries

We conclude that the norepinephrine stimulated contractile reserve of hearts with chronic coronary occlusion was comparable to that of normal hearts, however norepinephrine forced these hearts to spend the entire flow reserve of the remaining normal artery while producing ischemia in collateral dependent areas The same dose of norepinephrine did not require the entire flow reserve of normal dogs

REFERENCES

1 Helfant, R. H., Vokonas, P S., and Gorlin R. Functional importance of the human coronary collateral circulation N Engl. J Med. 284 1277 1971
2. Lavine P Filip Z., Najmi, M., Kimbiris, D., Segal, B L. and Linhart, J W Clinical and hemodynamic evaluation of coronary collateral vessels in coronary artery disease AM HEART J 87,343 1974
3 Knoebel, S B., McHenry P L., Phillips, J F., and Pauletto F J Coronary collateral circulation and myocardial blood flow reserve, Circulation 46 84 1972.
4 Harris, C N., Kaplan, M. A., Parker D P., Aronow W S., and Ellestad M H. Anatomic and functional correlates of intercoronary collateral vessels, Am. J Cardiol. 30 611 1972
5 Rosenfeldt, F L., Gill, C C Wechsler A. S., and Sabiston D C Ventricular function following experimental coronary artery bypass grafting The relation of functional improvement to haemodynamics in the graft Cardiovasc Res. 8 [illegible] 1974
6 Schaper W The collateral circulation of the heart, New York 1971 North Holland American Elsevier Publishers
7 Flameng, W and Schaper W Multiple coronary occlusion without infarction Effects of heart rate and vasodilation AM HEART J 85 767 1973
8 Flameng, W., Wusten, B Winkler B., Pasyk, S., and Schaper W Influence of perfusion pressure and heart rate on local myocardial flow in the collateralized heart with chronic coronary occlusion AM HEART J 89 51 1975
9 Kettler D., Cott, L Hensel, I., Martel, J., and Bretschneider H J Combination of piritramide and N O a new anaesthetic method for studies of cardiovascular function in dogs, Pflugers Arch. Ges. Physiol. 319 42, 1970
10 Buckberg, G D., Luck, J C., Payne J B Hoffmann, J I. E Archie J P and Fixler D E Some sources of error in measuring regional blood flow with radioactive microspheres J Appl Physiol. 31 598, 1971
11. Domenech, R. J Hoffmann J I. E Noble M J M., Saunders K B and Subijanto S Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs Circ. Res. 25 581 1969
12. Utley J Carlson, E L Hoffmann J I E., Martinez, H M and Buckberg G D Total and regional myocardial blood flow measurements with 25 μ, 15 μ, 9 μ, and filtered 1 10 μ diameter microspheres and antipyrine in dogs and sheep Circ Res. 34 391 1974
13 Schaper W Lewi, P., and Flameng W Myocardial steal produced by coronary vasodilation in chronic coronary artery occlusion Basic Res. Cardiol. 68 3 1973
14 Veragut, U P., and Krayenbuehl, H P Estimation and

maximal vasodilation the flow distribution is nonhomogeneous, with the endocardium supplied by collaterals being the least well perfused area [8]

During norepinephrine infusion the coronary blood flow in normal dogs increases together with the oxygen consumption This increase, however, is not homogeneous, the subendocardial layers are more dilated than the subepicardial ones (endo/epi ratio 1 5 compared to 1 0 in control) This suggests that the endocardium during norepinephrine infusion has a higher oxygen consumption The effect of norepinephrine in the coronary circulation is a matter of dispute Pitt and associates[23] and Vatner and associates[24] demonstrated the existence of alpha receptors in the canine coronary arteries in the conscious dog In the anesthetized dog, however several authors were unable to show alpha receptor activity in the coronary arteries [24, 25] Berne [6] demonstrated in the beating or fibrillating dog heart an initial decrease of coronary blood flow followed by a longer lasting increase reflecting increased myocardial metabolism In our study myocardial blood flow was measured by tracer microspheres when a steady state after norepinephrine infusion was reached so that any vasoconstricting effect of norepinephrine is probably absent

During norepinephrine stress the coronary bed of normal dogs was not maximally dilated because there was still a supplementary increase in flow after reactive hyperemia plus norepinephrine In dogs with multiple chronic coronary occlusions however, the norepinephrine infusion leads to maximal coronary dilation There is no longer any difference in blood flow distribution during norepinephrine alone and NE plus reactive hyperemia (Fig 3) This means that the flow to the nonoccluded area of the left ventricle is as high as in normal dogs during norepinephrine plus reactive hyperemia The collateral resistance however, impedes flow to the occluded area at a certain level During norepinephrine infusion, this level was not high enough in our group of constrictor dogs to balance oxygen demand and supply by compensatory flow increase the subendocardial flow was significantly lower in the collateral dependent region compared with the same area in normal hearts This implies that the collateral dependent subendocardium is ischemic during norepinephrine infusion After aortocoronary bypass the normal conditions of flow distribution are restored The flow in the nonoccluded area decreases and the flow to the collateral-dependent myocardium increases to approximately the same level as in normal dogs.

A possible explanation for this flow redistribution during norepinephrine in hearts with chronic coronary artery occlusions and collaterals is as follows Because of the relative ischemia in the collateralized area during stress the local contractility decreases To compensate for this decrease the contractility in the nonoccluded area increases, reflected by an increased myocardial flow above the normal levels A strong argument for this hypothesis is the fact that overall contractility in the heart with chronic coronary artery occlusions is quite normal It has to be considered, however, that norepinephrine is not a maximal stress for myocardial contractility in the normal dog heart, because the coronary reserve is not completely expended during norepinephrine infusion (Fig 3) The fact that a greater increase in contractility in the "normal" myocardium is achieved with the same dose of norepinephrine in dogs with chronic coronary artery occlusions needs some further discussion

A possible explanation could be that the myocardium in animals with chronic coronary artery occlusions is more sensitive to norepinephrine than normal ones Our finding, however, that after coronary bypass the myocardial blood flow normalizes makes this argument unlikely Theroux and associates [7] found direct evidence of a regional Frank Starling effect after acute coronary artery occlusion in the normal myocardium. In our experiments it is hard to believe that the degree of ischemia is great enough to produce a bulging in the collateral dependent myocardium

It is concluded that the development of a collateral circulation in dogs with chronic coronary artery occlusions has a protective effect on myocardial performance Although contractile reserve is in the normal range, coronary flow reserve during norepinephrine infusion is completely expended in areas supplied by normal arteries while collateral dependent myocardium becomes ischemic During stress, aortocoronary bypass normalizes myocardial blood flow distribution by reducing flow in the myocardium perfused by normal arteries and increasing flow in the myocardium previously supplied by collaterals

The effect of acute hypoxia on the viscoelastic properties of the myocardium

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It is a common clinical postulate that the heart becomes stiffer when subjected to hypoxic conditions.[1-4] Evidence for this change in the elastic properties of the myocardium is supplied by the observations that (1) the ratio of ventricular end diastolic pressure to end diastolic volume increases during attacks of angina pectoris[3] (2) there is a high incidence of S gallop rhythms during anginal attacks[1] (3) the amplitude of the A wave in the apex cardiogram is increased during the period of cardiac pain[2] The presumption that the alteration in cardiac stiffness is due to hypoxia and is not a manifestation of decreased blood flow is strengthened by the finding that myocardial stiffness is reduced within minutes after interruption of coronary flow to an area of the ventricle[5] Finally studies of isolated papillary muscles have suggested that the modulus of elasticity may increase when subjected to brief periods of hypoxia[6]

The mechanism whereby alterations in the oxygen supply to the myocardium could increase ventricular stiffness has not been settled Recent data from clinical studies in which angina attacks were provoked by atrial pacing[7] and the results from isolated papillary muscle studies presented here suggest that the increased muscle stiffness observed during episodes of acute hypoxia does not result from a change in the fundamental elastic behavior of the myocardium

Theory

The diastolic length tension relationship of the myocardium is nonlinear[8] and can be best described for an isolated papillary muscle in a one dimensional field by an exponential equation of the form

$$t = ae^{b\lambda} \qquad (1)$$

where t is the longitudinal tension within the muscle λ is the normalized length of the muscle fibers e is the base of the natural logarithm and a and b are constants This equation can also be used to describe the elastic properties of the intact ventricle by substituting ventricular pressure P for the tension term and ventricular volume V for the length term and changing the value of the constants a and b[9] Similar but more complicated stress-strain expressions for the elastic behavior of the intact heart that utilize the mid wall stress as calculated from either a spherical or ellipsoid model of the heart have been proposed.

Conversion of Eq (1) to the logarithmic form permits determination of the numerical value of the constant b as follows

$$lnt = lna + b\lambda \qquad (2)$$

$$b = (lnt - lna)/\lambda. \qquad (3)$$

This dimensionless ratio is the modulus of elasticity and represents the slope of the linear relationship between *lnt* and the muscle length λ.[6] The value of this constant increases with a decrease in the fundamental distensibility of the myocardial (which is the same as an increase in stiffness)

The *specific stiffness* of the myocardium that is the ratio $dt/d\lambda$ as calculated at a specific muscle length will increase exponentially with an increase in the length of the muscle due to the nonlinear nature of the length tension relationship (Eq [1]) Thus the greater the myocardium is stretched, the stiffer it becomes Mathematically the specific stiffness is the slope of a tangent to the exponential length tension curve at the specific muscle length under consideration The

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quantification of myocardial contractility in the closed chest dog Cardiologia 47 96 1965

15 Wallace A G Skinner N D Jr and Mitchell J H Haemodynamic determinants of the maximal rate of rise of left ventricular pressure Am J Physiol 205 30 1963

16 Patterson R E Kent B B and Peirce E C A comparison of empiric contractile indices in intact dogs Cardiology 57 277 1972

17 Wildenthal K Mierzwiak D S and Mitchell J M Effect of sudden changes in aortic pressure on left ventricular dp/dt Am J Physiol 216 185 1969

18 Fisher V J Lee R J Marlon A M and Kavaler F Paired electrical stimulation and the maximal contractile response of the ventricle Circ Res 20 520 1967

19 Schaper W K A Lewi P and Jagenau A H M The determinants of the rate of change of the left ventricular pressure (dp/dt) Arch Kreislauff 46 27 1965

20 Ross J Jr Covell J W Sonnenblick E H and Braunwald E Contractile state of the heart characterized by force velocity relations in variably afterloaded and isovolumic beats Circ Res 18 149 1966

21 Monroe R G Gamble W J La Farge C G Kumar A E and Manasek F J Left ventricular performance at high end diastolic pressures in isolated perfused dog hearts Circ Res 26 85 1970

22 Kumar R Hood W B Joison J, Norman J C and Abelmann W H Experimental myocardial infarction II Acute depression and subsequent recovery of left ventricular function serial measurements in intact conscious dogs, J Clin Invest. 49 55 1970

23 Pitt B Elliot E C and Gregg, D E. Adrenergic receptor activity in the coronary arteries of the unanesthetized dog Circ Res. 21 75 1967

24 Vatner S F Higgins, C B and Braunwald E Effects of norepinephrine on coronary circulation and left ventricular dynamics in the conscious dog Circ. Res. 34 812 1974

25 Hirche H Die Wirkung von Isoproterenol, Adrenalin, Noradrenalin und Adenosin auf die Durchblutung und den O Verbrauch des Herzmuskels vor und nach Blockierung der β Rezeptoren Pflugers Arch 288 162, 1966

26 Berne R M Effect of epinephrine and norepinephrine on coronary circulation Circ. Res 6 644 1958

27 Theroux P Franklin D Ross, J., Jr and Kemper W S Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog Circ. Res. 35 896, 1974

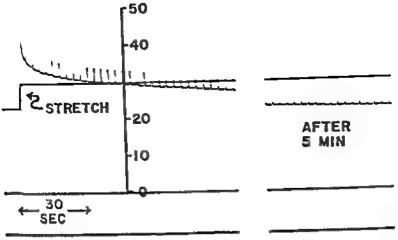

Fig 3 Sections of a typical record showing the myocardial tension response during and immediately after a quick stretch and after 5 minutes of stress relaxations. The periodic isometric contraction tension is superimposed on the resting tension the onset of stretch is indicated by the deviation of the top line calibration is in grams of force

A quick sustained stretch of the muscle was obtained by removing the block (*B*) and permitting the lever arm to be pulled by the weight (*W*) against the stop (*A*)

The papillary muscle was stimulated to contract isometrically throughout the experiment by maximal square wave stimuli delivered at a rate of [illegible] per minute from an electronic stimulator (*S*) After an equilibrium period of 45 minutes, each muscle was subjected to a series of three progressively larger stretches In each series the muscle was stretched in turn to a new length that was 10λ, 20λ and then 30λ where λ is the per cent elongation above control This was calculated from the relationship $\lambda = Ls/Lo \times 100$ where Ls is the magnitude of the stretch in millimeters and Lo is the resting muscle length in millimeters Each stretch was held for 5 minutes The muscle was then returned to its rest length and maintained at that length for 15 minutes before being subjected to the next stretch After completion of the control series of three stretches the solution in the chamber was changed to one that had been vigorously aerated with 95 per cent N_2-5 per cent CO for at least 45 minutes The muscle was permitted to equilibrate in this solution for 10 minutes The sequence of three stretches described above was then repeated This experimental period is referred to as the hypoxic period. During this interval the isometric contractile tension was reduced to about 20 per cent of its control value The control solution was then returned to the chamber After a second

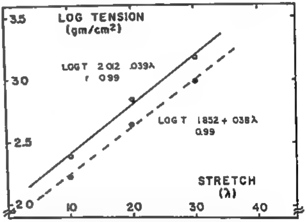

Fig 4 Semilog plot showing typical papillary muscle length tension relationship before (solid line) and after (dashed line) 5 minutes of stress relaxation

equilibration period of 10 minutes the muscle was subjected to a third series of three stretches This was designated the recovery period Isometric contractile tension returned during this period to an average of about 80 per cent of the control value

The papillary muscle was removed from the chamber at the end of the experiment blotted on filter paper and weighed The cross sectional area of the muscle was calculated by assuming it had a cylindrical shape and a density of 1 Gm (wt) per cubic centimeter The muscle tension recorded by the force transducer was expressed as grams per square centimeter

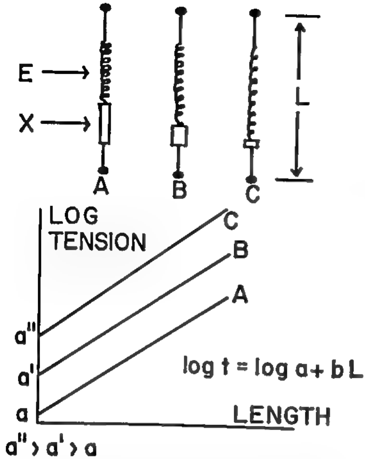

Fig 1 Above model of a cardiac muscle in which all the elastic properties are condensed into a single elastic unit E This elastic unit is in series with an unspecific element X A B and C show the effect of changing the length of the X unit on the length of the elastic element of this model while holding the over all muscle length constant Below the effect of changing the length of the X series unit as shown above in A B and C on the log tension intercept of the semilog stress strain curve See text for discussion

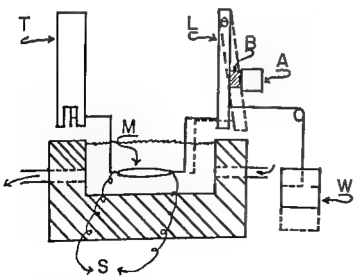

Fig 2 Schematic drawing of the experimental apparatus and muscle bath See text for description of the various parts and discussion of their use

equation for this value can be determined by differentiating Eq (1) with respect to λ as follows

$$dt/d\lambda = abe^{b\lambda} = bt \quad (4$$

The value of lna in Eq (2) represents the tension intercept of the linearized length tension relationship The value of this constant can be simply determined from the logarithmic form of the length tension relationship, as follows

$$lna = lnt - b\lambda \quad (5$$

In the studies reported here, lna has been converted from the natural logarithm to the common logarithm form using the base 10 for ease of plotting and is given in the form log a

The significance of changes in the value of log a can be interpreted by considering the muscle model shown in Fig 1 In this model all of the elastic properties of the muscle are condensed into a single elastic unit, E, that is in series with a second unit, X The anatomical analogue of this second unit is not defined, however, it could be the contractile element of the muscle as defined in Hill s[11] original model When the model shown in Fig 1 is stretched and then maintained at a fixed length, L the tension developed by the stretched elastic unit will be inversely related to the length of the X unit This example suggests that an increase in the value of the constant log a (or lna in Eq [5]) is consistent with a decrease in the length of the X unit in the model that is in series with the elastic element of the muscle

Method

The left anterior papillary muscle of the rabbit was utilized in these studies The beating heart was opened under modified Ringer Locke solution that had been aerated with 95 per cent O_2-5 per cent CO_2 This solution contained (in millimoles per liter) Na 145 2, K , 5 8 Ca 2.0, Mg 1 2, Cl 127 8 SO_4 1 2 PO_4 1 0, HCO_3 27 2 glucose 11 1 The pH was 7 41 and the temperature was maintained at 30° C The papillary muscle was arranged for study in a chamber containing the same Ringer Locke solution This solution was changed frequently during the experiment The apparatus used to apply a prolonged stretch to the muscle and to measure its tension has been described[12] In these experiments the apparatus was slightly modified as shown in Fig 2 so that one end of the muscle (M) was attached to the force transducer (T) and the other end was connected to the lever system (L)

shown in Fig 4 The average correlation coefficient of the regression equation of all the length tension plots was 0.94 (range 1 00 to 0 81) The average values of the constants log a and b for the semilog length tension regression equations that were fitted to the data obtained during the control, hypoxia and recovery periods are shown in Fig 5

The parameters of the linearized length resting tension regression plots were subjected to statistical analysis to determine if they were different at a significant level of 0 05 The differences between the mean values of both log a and b for the control, hypoxia and recovery groups immediately after stretch were analyzed by means of Tukey's simultaneous range test [13] This procedure was also used to examine the change in log a that occurred with stress relaxation during each treatment group A standard F test for data variance and a paired t test were used to detect differences in data means after stress relaxation The results are summarized in Tables I II and III.

Discussion

The fall in myocardial tension during stress relaxation is usually considered to result from the slow elongation of a viscous unit that is in series with the elastic elements of the muscle This damped internal movement permits the elastic elements to shorten and muscle tension to fall even though the over all length of the muscle does not change The significant reduction reported here in the tension intercept of the myocardial length tension relationship after stress relaxation is in agreement with this concept. However the observation that the magnitude of the reduction in this parameter was smaller during the hypoxic period than during control was unexpected It is tempting due to the low oxygen level during this period to ascribe this change to a failure of some metabolic process Specific data on this point are not available however so that the significance of the smaller reduction in log a with stress relaxation in the hypoxia group cannot be interpreted

There was no significant change in the modules of distensibility of the length tension relationship as a result of stress relaxation This observation provides support for the concept that the elastic elements are only passively involved during this event and that the loss of muscle tension during stress relaxation does not result from a change in its elastic properties

The modulus of distensibility of the papillary muscle was not significantly different during the hypoxic period than during either the control or recovery periods. Similar observations were reported by Berry and associates [7] who calculated a distensibility modulus for the left ventricle of nine patients before during and after periods of angina pectoris

The exponential nature of the length tension curve may offer a clue to the reported increase in the apparent stiffness of the myocardium during clinical episodes of decreased oxygenation Berry and associates found that the value of the log tension intercept of the length tension relationship was significantly increased during attacks of angina. This finding would be consistent with the development of increased myocardial tone by contraction of some unit in series with the elastic elements The result of such a sustained contraction—or perhaps it might be considered a failure of relaxation—would be to shift the stress strain curve to the left and thus cause the specific stiffness at comparable muscle length to be increased. This is an attractive hypothesis which makes our finding of a higher average value for the log a parameter of the length tension relationship during hypoxia appear to have meaning Unfortunately the variability of the individual data does not permit these average values to be considered statistically different at a p value of 5 per cent and we are not able to confirm the findings of Berry and associates on this point

The average calculated cross sectional area of the papillary muscles utilized in these studies was slightly larger than the 1 mm ^{2} limits suggested by Greenspan and Cranefield[14] for the diffusion of oxygen to occur throughout the fiber This however was not considered to be a serious problem as each muscle served as its own control and any tendency for core dysfunction would also be subtracted from the experimental and recovery data

Summary

The viscoelastic properties of the isolated rabbit papillary muscle were studied by constructing a semilogarithmic length tension curve before and after it had undergone 5 minutes of stress relaxation before during and after exposure to a solution aerated with 95 per cent

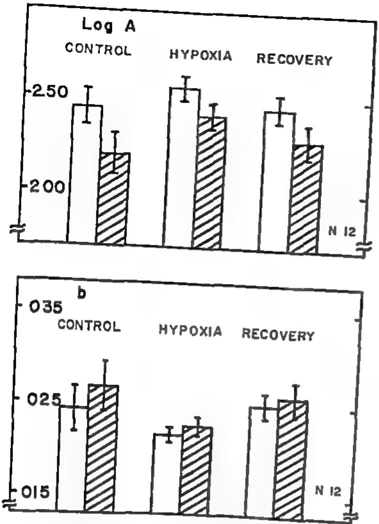

Fig 5 Average values for the length tension parameters log A and B before (solid line) and after stress relaxation (dashed line) during control hypoxia and recovery The vertical line indicates 1 standard error of the mean

Results

Papillary muscles from 12 hearts were utilized in this study The average length was 5 20 mm, with a standard error of 0 28 mm The averaged calculated cross section area was 1 30 mm ^{2}, with a standard error of 0 16 mm ^{2} A typical record of the change in muscle tension following a stretch is shown in Fig 3 The resting tension rose abruptly to its peak value when the muscle length was increased, the tension then fell exponentially with time as long as the muscle was held at its new length The loss of tension due to stress relaxation was assumed to be complete at the end of 5 minutes The periodic alterations in muscle tension superimposed on the rest tension seen in Fig 3 are due to the isometric twitch contraction of the papillary muscle

Resting muscle tension was measured just before the onset of a twitch contraction at two points following each stretch (1) immediately after stretch and (2) after 5 minutes of stress relaxation had taken place These tension values were used to construct length tension curves that represented the diastolic behavior of the muscle both before and after stress relaxation during each treatment period An example of such a plot, shown in the semilog linear form, that illustrates the length tension relationship before and after stress relaxation during a control experiment is

Table I Summary of statistical analysis of the parameters of the length tension relationship of the rabbit papillary muscle subjected to various conditions before and after stress relaxation

Comparison	F test for variance		t test for difference	
	F	Sig p 0 05	T	Sig p 0 05
Slope (b)				
Control vs control S R	1 313	No	0 69?	No
Hypoxia vs hypoxia S R	2.000	No	0 819	No
Recovery vs. recovery S R	1 0?4	No	0.133	No
Tension intercept (log a)				
Control vs control S R	1 292	No	8 432	Yes
Hypoxia vs. hypoxia S R	1 5?4	No	? 436	Yes
Recovery vs recovery S R	1 696	No	6 9422	Yes

S R = After stress relaxation

Table II Summary of Tukey s simultaneous range test of the mean values of log a and b for the three treatment groups

Group	$\bar{X}$	Range	LSR	Sig
Log a				
Control	2 4350	$\bar{X}_H - \bar{X}_C$ = 0 1139		No
Hypoxia	2 5489	$\bar{X}_H - \bar{X}_R$ = 0 1065	0 26?2	No
Recovery	2 4424	$\bar{X}_C - \bar{X}_R$ = 0 0074		No
Log b				
Control	0 0242	$\bar{X}_H - \bar{X}_C$ = 0 00?6		No
Hypoxia	0 0216	$\bar{X}_H - \bar{X}_R$ = 0 0034	0 0057	No
Recovery	0 0250	$\bar{X}_C - \bar{X}_R$ = 0 0008		No

LSR = Least significant range.

Table III Analysis of the change in log a with stress relaxation between treatment groups

Group	$\bar{X}$	Range	LSR	Sig
Log a				
Control	0 2524	$\bar{X}_H - \bar{X}_C$ = 0 1060		Yes
Hypoxia	0 1464	$\bar{X}_H - \bar{X}_R$ = 0 0245	0 084?	No
Recovery	0 1701	$\bar{X}_C - \bar{X}_R$ = 0 0815		No

Effects of acetylsalicylic acid, dipyridamole and hydrocortisone on epinephrine induced myocardial injury in dogs

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Myocardial calcium and sodium concentrations increase and potassium and magnesium concentrations decrease in damaged or infarcted myocardium when compared to normal myocardium. Even more striking is the increase in radiocalcium uptake most notably into the mitochondria in acutely damaged myocardium. These increases in myocardial calcium concentrations and radiocalcium uptakes into myocardium more specifically into the mitochondrial fraction appear to provide accurate indices of irreversible myocardial injury which might be used to quantify the cardioprotective effects of various agents or maneuvers advocated as therapy in acute myocardial infarction.

Difficulty was encountered in inducing reproducible myocardial infarction in dogs by surgical ligation of coronary arteries.* Infusions of sympathetic catecholamines (isoproterenol, epinephrine and norepinephrine) have been reported to produce diffuse myocardial necrosis in small animals.* A diffuse and reproducible myocardial necrosis has been produced in dogs by infusion of large amounts of epinephrine over a 6 hour period. After establishing a suitable model for producing and objectively quantifying myocardial damage, the cardioprotective effects of three agents previously reported to have beneficial effects in acute myocardial infarction, namely acetylsalicylic acid (ASA),* dipyridamole (Persantin)[21] and hydrocortisone,[22] were tested.

Methods

Mongrel dogs weighing 17 to 25 kilograms were anesthetized with pentobarbital (25 mg. per kilogram) and were given small supplements as necessary to maintain anesthesia. An endotracheal tube was inserted and the animals were ventilated with a Harvard respirator. A femoral vein was cannulated for infusions and the femoral artery for blood pressure measurements and blood collections. Electrocardiograms were monitored and recorded hourly with the arterial blood pressures.

The first series of studies was designed to compare the effects of epinephrine and calcium chloride against isotonic sodium chloride (control) infusions. For these studies, three groups of animals were utilized.

Control group. Isotonic (0.9 per cent) sodium chloride was infused into each of the four animals at the rate of 2 c.c. per minute for 6 hours.

Epinephrine group. Epinephrine (4 μg per kilogram per minute) was infused into each of seven animals in isotonic saline at the rate of 2 c.c. per minute for 6 hours.

Calcium group. Calcium chloride (200 mg. per kilogram per 6 hours) was infused into each of the four animals in isotonic saline at the rate of 2 c.c. per minute for 6 hours.

The second series of studies was designed to compare the protective effects of three agents (acetylsalicylic acid, dipyridamole, or hydrocorti-

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nitrogen and 5 per cent carbon dioxide Stress relaxation was accomplished in each treatment group by a reduction in the tension intercept of the log length tension curve without significant change in its slope There was no significant change in either of these parameters between the control, hypoxia, and recovery groups These findings lead to the conclusions that (1) the loss of muscle tension during stress relaxation is not due to a change in the elastic properties of the myocardium and (2) hypoxia does not increase the fundamental stiffness characteristics of the cardiac muscle

I am grateful for the technical assistance of Mrs Sandra Caggiano and Mr Gerald Merritt.

REFERENCES

1 Fowler N O Angina pectoris clinical diagnosis Circulation 46 1079 1972

2. Martin C E Shaver J A and Leonard J J Physical signs, apex cardiograph, phonocardiography and systolic time intervals in angina pectoris Circulation 46 1098 1972

3 Dwyer E M Jr Left ventricle pressure–volume alterations and regional disorders of contraction during myocardial ischemia induced by arterial pacing Circulation 42 1111, 1970

4 Mirsky I Cohn P F Levine J A Gorlin R Herman M V Kreulen T H and Sonnenblick E H Assessment of left ventricular stiffness in primary myocardia disease and coronary artery disease Circulation 50 128 1974

5 Forrester, J S Diamond, G Parmley W W and Swan H J C Early increase in left ventricular complianc following myocardial infarction J Clin Invest. 51 598 1972

6 Templeton G H Adcock, R C and Willerson, J T Influence of hypoxia on isolated papillary muscle stiffness and its elastic and viscous components Circulation 47 (Suppl. 4) 67 1973

7 Berry W H Brooker J F., Alderman E L, and Harrison D C Changes in diastolic stiffness and tone of the left ventricle during angina pectoris Circulation 49 255, 1974

8 Diamond G Forrester J S, Hargis, J and Pharmley W W Diastolic pressure volume relationship in the canine left ventricle Circ. Res. 24 267 1971

9 Gaasch, W H Battle W E Oboler A. A., Banas J S Jr and Levine H J Left ventricle stress and compliance in man Circulation 45 746 1972

10 Little R. C and Wead, W B Diastolic viscoelastic properties of active and quiescent cardiac muscle, Am J Physiol 221 1120 1971

11 Hill A V Mechanics of active muscles, Proc. R Soc Lond Ser B141 104 117 1953

12. Little R. C Dynamics of stress relaxation in skeletal muscle Am J Physiol. 217 1665 1969

13 Sokal, R. B and Rohlf F S Biometry the principle and practice of statistics in biological research San Francisco 1969 W H Freeman and Company p. 238.

14 Greenspan K and Cranefield P F Influence of some factors on oxygen uptake of canine cardiac Purkinje fibers Am J Physiol 204 5 1963

Effects of acetylsalicylic acid, dipyridamole, and hydrocortisone on epinephrine induced myocardial injury in dogs

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Myocardial calcium and sodium concentrations increase and potassium and magnesium concentrations decrease in damaged or infarcted myocardium when compared to normal myocardium.[1] Even more striking is the increase in radiocalcium uptake, most notably into the mitochondria, in acutely damaged myocardium.[1] These increases in myocardial calcium concentrations and radiocalcium uptakes into myocardium, more specifically into the mitochondrial fraction, appear to provide accurate indices of irreversible myocardial injury which might be used to quantify the cardioprotective effects of various agents or maneuvers advocated as therapy in acute myocardial infarction.

Difficulty was encountered in inducing reproducible myocardial infarction in dogs by surgical ligation of coronary arteries.[1] Infusions of sympathetic catecholamines (isoproterenol, epinephrine, and norepinephrine) have been reported to produce diffuse myocardial necrosis in small animals.[1-6] A diffuse and reproducible myocardial necrosis has been produced in dogs by infusion of large amounts of epinephrine over a 6 hour period. After establishing a suitable model for producing and objectively quantifying myocardial damage, the cardioprotective effects of three agents previously reported to have beneficial effects in acute myocardial infarction, namely, acetylsalicylic acid (ASA),[illegible] dipyridamole (Persantin),[21] and hydrocortisone,[22-24] were tested.

Methods

Mongrel dogs weighing 17 to 25 kilograms were anesthetized with pentobarbital (25 mg. per kilogram) and were given small supplements as necessary to maintain anesthesia. An endotracheal tube was inserted and the animals were ventilated with a Harvard respirator. A femoral vein was cannulated for infusions and the femoral artery for blood pressure measurements and blood collections. Electrocardiograms were monitored and recorded hourly with the arterial blood pressures.

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Table I Myocardial concentrations (mg /100 Gm fat free dry weight) of sodium, potassium, calcium, magnesium, zinc, and copper, and of serum calcium and SGOT concentrations in animals receiving epinephrine or calcium chloride infusions compared to saline control infusions (all values, mean ± S E M)

	Control	*Epinephrine*	*Calcium chloride*
No of animals	4	7	4
Sodium	408 ± 33	646 ± 42*	454 ± 60
Potassium	1 320 ± [illegible]	1 071 ± 78	1 326 ± 14
Calcium	5 0 ± 0 9	12 0 ± 1 1 *	7 9 ± 0 9
Magnesium	[illegible] ± 4	69 ± 5	77 ± 2
Zinc	6 1 ± 0 1	5 4 ± 0 5	6 2 ± 0 2
Copper	1 6 ± 0 1	1 4 ± 0 3	1 8 ± 0 4
Serum calcium (mEq /L)			
0 hr	4 5 ± 0 2	4 7 ± 0 2	4 7 ± 0 2
6 hr	4 3 ± 0 2	4 3 ± 0 2	6 6 ± 0 5*
SGOT 0 hr	25 ± 5	18 ± 2	17 ± 3
Karman activity units 6 hr	20 ± 2	202 ± 30	16 ± 1

$p < 0\,05$ $^*p < 0\,01$ $p < 0\,001$

sone) in prevention of epinephrine induced myocardial injury

Acetylsalicylic acid group ASA (600 mg) was given orally twice daily for 4 days to each of six animals prior to the epinephrine infusion described above

Dipyridamole group Dipyridamole (50 mg) was given orally twice daily for 4 days to each of six animals prior to the epinephrine infusion

Hydrocortisone group Hydrocortisone (50 mg per kilogram) was infused simultaneously with the epinephrine over the 6 hour period of infusion

All animals received 200 μCi of radiocalcium just prior to initiation of the epinephrine or calcium infusion A 10 c c blood sample was drawn initially and at hourly intervals after starting the infusion for serum glutamic oxalacetic transaminase (SGOT) creatine phosphokinase (CPK), calcium and blood gas determinations

After completion of the infusion all dogs were killed with Anectine and Nembutal The hearts were rapidly removed, placed in cellophane containers, and immersed in ice Three samples of left ventricle were removed consistently from the same area and used immediately for the radiocalcium uptake and histology studies or stored frozen for the cation concentration studies Th first myocardial sample was processed for ligh microscopic evaluation with hematoxylin an eosin stains The second myocardial sample wa utilized to determine concentrations of sodiu potassium, calcium, magnesium, zinc, and coppe with techniques previously described[7,8] Sampl (1 to 2 Gm) were weighed wet, dried at 105° C and reweighed The dried tissue was digested wit 10 ml of a mixture of nitric, sulfuric, and perchlo ric acid-strontium solution With each run o samples, a blank acid mixture was treated in similar fashion and analyzed Cation concentra tions of this blank then were subtracted from th corresponding metals of each sample an expressed in milligrams per 100 Gm of fat fre dry weight

An aliquot of this solution was utilized t quantify zinc and copper concentrations on th Perkin Elmer 303 atomic absorption spectropho tometer, with the use of the three slot Bolin burner head with acetylene as the fuel an compressed air as the oxidizer Aliquots of th original solution were further diluted to measu calcium, magnesium sodium, and potassiu concentrations After linearity was establishe with standard solutions prepared in the sam diluent, the concentrations of all four divalen cations were recorded on the direct concentratio readout attachment Sodium and potassiu concentrations were quantified with a flam photometer (Instrumentation Laboratories)

The third myocardial sample was used fo radiocalcium uptake and differential ultracentri ugation studies by means of techniques previou ly described[7] Myocardium was homogenized i 0 25M sucrose and filtered through a 4 by 4 inc gauze pad to remove muscle fibers The filtrate were ultracentrifuged in a Beckman L 4 ultracen trifuge for 10 minutes at 700 g and the pelle which contained the nuclear fraction was isolate and weighed The remaining homogenate wa centrifuged for 60 minutes at 5,000 g This pelle contained the mitochondrial fraction a mixtur of mitochondria and lysosomes The remainin homogenate again was centrifuged for 60 minute at 55 000 g and the pellet which contained th microsomal fraction, a mixture of ribosomes an sarcoplasmic reticulum, was separated Finally the remaining homogenate was spun for 17 hour at 80 000 g This pellet contained soluble protein (DNA RNA immunoglobulins, albumin en

-ymes) not attached to sarcoplasmic reticulum The remaining supernatant was monitored in the analytic ultracentrifuge and found to be free of protein. Electron microscopic appearances of pellets collected from infarct peri infarct and normal heart have been monitored and reported previously [7]

Means and standard errors of the means were determined with standard statistical techniques Student s paired and unpaired t tests were utilized to test the statistical significance of observed differences.

Results

The mean (± S E M) concentrations of sodium potassium calcium and magnesium per 100 Gm of fat free dry weight of myocardium and serum calcium and SGOT concentrations for the control calcium chloride and epinephrine infusion groups of animals are tabulated in Table I. Myocardial sodium and calcium concentrations increased ($p < 0.01$) and potassium and magnesium concentrations decreased ($p < 0.01$) when the group receiving epinephrine infusions was compared against the control group Serum SGOT concentrations also were increased significantly ($p < 0.01$) No significant differences in any myocardial cation concentration was observed in the calcium chloride infusion animals compared to control animals The serum calcium concentrations were significantly increased ($p < 0.01$) over those observed in the control animals.

Ca uptakes into intact myocardium and each of its subcellular components (nuclear mitochondrial, microsomal soluble protein) of epinephrine calcium chloride and control groups are shown in Table II Significant increases ($p < 0.05$) in radiocalcium uptakes were found in intact myocardium and in all subcellular fractions in the epinephrine infused animals compared against the control animals The Ca uptakes into intact myocardium and the subcellular components tended to be lower in the calcium chloride-infused animals but the decrease was significant ($p < 0.01$) only in the microsomal fraction.

A comparison of the morphologic evidence of myocardial damage in the first three groups is shown in Table III Evidence of myocardial damage was graded without prior knowledge of treatment by one observer (D J B) as normal

Table II Radiocalcium (Ca) uptakes (no of counts per minute per gram of dried tissue or fraction) into intact myocardium and each of its subcellular components (nuclear mitochondrial, microsomal soluble protein) in animals receiving epinephrine or calcium chloride infusions compared to saline control infusions (all values mean ± S E M)

	Control	*Epinephrine*	*Calcium chloride*
No of animals	4	7	4
Nuclear	317 ± 40	2 148 ± 463	243 ± 25
Mitochondrial	827 ± 6	4 957 ± 324	599 ± 194
Microsomal	"51 ± 86	3,158 ± 568	3,6 ± 44
Soluble protein	4"9 ± 136	[illegible]085 ± 497	223 ± 49
Intact myocardium	334 ± 57	2,560 ± 883	242 ± 16

$p < 0.05$ $p < 0.01$ $p < 0.001$

Table III Histologic evaluation (hematoxylin and eosin stain) of myocardial structure in control epinephrine infusion and calcium chloride infusion animals

Histologic evaluation	*Control*	*Epinephrine*	*Calcium chloride*
No of studies	4	7	4
Normal	4	0	2
Slight change	0	0	2
Moderate change	0	2	0
Marked change	0	5	0

slight moderate and marked change examining the section for (1) loss of striation and fracture of myocardial fibers (2) nuclear swelling and distortion (3) inflammatory cell infiltration and (4) abnormalities in staining (eosinophilia) All four control hearts were classified morphologically as normal. The animals received calcium chloride infusions were evenly divided between normal and slight change histologically Five of seven animals receiving epinephrine infusions were found to have marked changes the other two had moderately severe changes

The second series of studies compared the effects of pretreatment with ASA or dipyridamole or simultaneous infusion of hydrocortisone against the effects of epinephrine infusions alone (Table IV) Myocardial calcium concentrations in animals pretreated with dipyridamole or given simultaneous infusions of hydrocortisone are

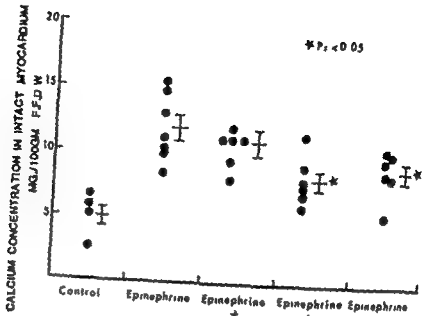

Fig 1 Calcium concentrations in intact myocardium obtained from saline infused control dogs from epinephrine-infused dogs from epinephrine infused dogs pretreated with acetylsalicylic acid (aspirin) or dipyridamole and from epinephrine infused dogs receiving hydrocortisone simultaneously Student s t tests were used to compare each of the three treatment groups with the group receiving epinephrine alone

Table IV Myocardial concentrations (mg /100 Gm fat free dry weight) of sodium, potassium, calcium magnesium zinc and copper and of serum calcium SGOT, and CPK concentrations in animals receiving epinephrine compared to animals pretreated with acetylsalicylic acid or dipyridamole or given hydrocortisone simultaneously (all values mean ± S E M)

	Epinephrine	*Acetylsalicylic acid*	*Dipyridamole*	*Hydrocortisone*
No of studies	7	6	6	6
Sodium	646 ± 42	880 ± 139	70? ± 88	7?3 ± 61
Potassium	1 071 ± 78	1 158 ± 39	1 311 ± 55	1 297 ± 1*
Calcium	12 0 ± 0 1	11 2 ± 1 0	8 3 ± 0 8*	8 9 ± 0 8*
Magnesium	69 ± ?	81 ± 4	83 ± 3	78 ± 3
Zinc	5 4 ± 0 5	6 1 ± 0 2	6 9 ± 0 9	6 6 ± 0 ?
Copper	1 4 ± 0 3	1 5 ± 0 1	1 8 ± 0 4	1 5 ± 0 1
Serum calcium (mEq /L)				
0 hr	4 7 ± 0 2	4 3 ± 0 1	4 3 ± 0 1	4 3 ± 0 1
6 hr	4 3 ± 0 2	4 2 ± 0 1	4 2 ± 0 2	4 1 ± 0 2
SGOT 0 hr	18 ± 2	25 ± 4	22 ± 5	19 ± 3
Karman activity units 6 hr	202 ± 30	168 ± 21	169 ± 2?	17? ± 29
CPK				
0 hr	7 ± ?	17 ± 6	5 ± 1	10 ± 1
6 hr	221 ± 11	189 ± 41	122 ± 44	1?7 ± 36

*p < 0 05

significantly decreased (p < 0 05) compared to the animals receiving epinephrine infusions alone the decrease in the ASA treated groups was not statistically significant (Fig 1) The myocardial potassium concentrations also were significantly increased (p < 0 05) in the dipyridamole and hydrocortisone treated animals and the magnesium was increased (p < 0 05) in the dipyridamole treated animals No significant differences were observed in the serum calcium or SGOT concentrations in the three treated groups compared to the epinephrine infusion alone group Radiocalcium uptakes into the mitochondrial fraction decreased significantly (p < 0 01) in all three treated groups compared to the epinephrine alone group (Table V and Figure 2)

Morphologic changes in the three treated groups were compared to those observed in the group of animals receiving epinephrine infusion alone (Table VI) In contrast to the latter group where all seven animals showed moderately severe to marked changes only half of the ASA and hydrocortisone treated groups and only one in six of the dipyridamole treated group had this much damage morphologically Half of the dipyridamole treated animals were felt to have normal myocardium

The mean blood pressure levels in the epinephrine-infused animals rose from 127 ± 2 mm Hg to a peak of 176 ± 7 mm Hg 2 hours later and then fell gradually to 145 ± 19 mm Hg at the end of 6 hours Mean heart rates increased from 100 ± 6 beats per minute to 158 ± 9 at 1 hour and then rose slowly to 190 ± 14 at 6 hours No significant changes were observed in control animals during the 6 hour infusion period In the ASA treated group the terminal blood pressures tended to be higher and pulse rates lower and in the dipyridamole-treated group the terminal blood pressures tended to be lower and heart rate higher however these differences were not statistically significant Serial electrocardiograms (lead II) showed, in addition to the tachycardia progressive ST segment elevation in the epinephrine infused animals over the 6 hour period of study These changes were not observed in the animals in the three treatment groups

Discussion

Shen and Jennings[23] found myocardial calcium concentrations and radiocalcium uptakes greatly increased after coronary artery occlusion for 40 minutes (irreversible injury) followed by perfusion with arterial blood for 20 minutes No changes were found after shorter periods of ischemia (reversible injury) or when the injured myocardium was not reperfused with arterial blood. Furthermore those investigators were able to demonstrate with the electron microscope distinctive dense bodies in mitochrondria from injured reperfused myocardium Calcium and phosphate concentrations in isolated mitochondria also were greatly increased They concluded that the uptake of calcium was a feature of irreversible cellular injury but it occurred only when arterial blood flow was re established

Previous studies reported from our laboratory also showed that a marked increase in radiocalcium uptake and calcium concentrations were found in the infarcted myocardium of dogs with acute infarction produced by ligation of the left anterior descending coronary artery Furthermore the increased radiocalcium uptake was most striking and consistent in the mitochondrial fraction Unfortunately the area of infarcted or damaged myocardium produced by ligation of the coronary artery was extremely variable as determined by radiocalcium uptakes myocardial calcium concentrations serum enzyme concentrations (SGOT) and histologic evaluation To test the efficacy of various cardioprotective agents and maneuvers a more reproducible form of myocardial injury had to be developed This led to consideration of the use of sympathomimetic amines to produce a more diffuse myocardial injury

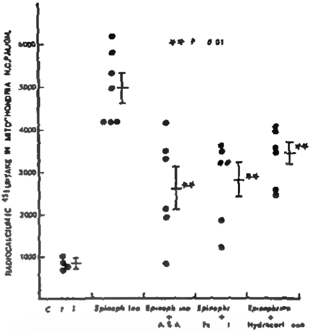

Fig 2 Radiocalcium uptake into the mitochondrial fraction obtained from saline-infused control dogs, from epinephrine-infused dogs, from epinephrine-infused dogs pretreated with acetylsalicylic acid (aspirin) or dipyridamole and from epinephrine infused dogs receiving hydrocortisone simultaneously Student's t tests were used to compare each of the three treatment groups with the group receiving epinephrine alone

Fleckenstein and his associates[3] have shown that large doses of sympathomimetic amines most notably isoproterenol administered to rats markedly increase transmembrane influx of calcium regardless of origin and are highly cardiotoxic initiating a breakdown and depletion

Table V Radiocalcium (^{45}Ca) uptakes (No of counts per minute per gram of dried tissue or fraction) into intact myocardium and each of its subcellular components in animals receiving epinephrine only compared to animals pretreated with acetylsalicylic acid or dipyridamole or given hydrocortisone simultaneously (all values, mean ± S E M)

	Epinephrine	*Acetylsalicylic acid*	*Dipyridamole*	*Hydrocortisone*
No of studies	7	6	6	6
Nuclear	2 148 ± 463	1 149 ± 234	863 ± 152	1 415 ± 195
Mitochondrial	4 957 ± 324	2 682 ± 505**	2 803 ± 400	3 424 ± 280
Microsomal	3 158 ± 568	2 349 ± 509	1 256 ± 319	2 619 ± 295
Soluble protein	2 085 ± 497	1 580 ± 471	667 ± 219*	1 403 ± 251
Intact myocardium	2 860 ± 883	1 070 ± 211*	661 ± 133	1 [illegible]50 ± [illegible]81

p < 0 05   p < 0 01

Table VI Histologic evaluation (hematoxylin and eosin stain) of myocardial structure in animals infused with epinephrine alone and those pretreated with acetylsalicylic acid or dipyridamole or given hydrocortisone simultaneously

Histologic evaluation	*Epinephrine*	*Acetyl salicylic acid*	*Dipyridamole*	*Hydro cortisone*
No studies	7	6	6	6
Normal	0	0	3	0
Slight change	0	3	2	3
Moderate change	2	1	1	1
Marked change	5	2	0	2

of high energy phosphate ATP and creatine phosphate with resultant myocardial necrosis They studied a number of agents which either potentiated or sensitized the myocardium to increased calcium uptake and myocardial damage and others which antagonized or protected against these changes

A dog model has been developed using infusions of pharmacological doses of epinephrine over a 6 hour period In this model, the uptake of radiocalcium into the mitochondrial fraction appeared to provide the most sensitive index of the extent of irreversible myocardial injury Myocardial concentrations of total calcium also were significantly increased in these animals

One potential explanation for the striking influx of calcium into myocardial cells might be that epinephrine produces a transient increase in serum calcium concentrations To test the effects of an acute increase in serum calcium concentrations on transmembrane calcium influx the serum calcium levels were increased measurably (4 7 to 6 6 mEq per liter) with an infusion of calcium chloride over a similar 6 hour period N increase in radiocalcium uptake was observed i intact heart and the increase in myocardial calcium concentrations was not significant, indicating that changes in serum calcium concentrations do not importantly influence myocardial calcium influx

Acetylsalicylic acid,[21] dipyridamole,[1] and corticosteroids[2 24] all have been reported to have cardioprotective effects in experimental myocardial infarction ASA and dipyridamole decrease platelet aggregation and presumably prevent formation of thrombi in small vessels in the heart. They are particularly effective in preventing epinephrine induced platelet aggregation

Libby and associates[23] have shown that pharmacologic doses of hydrocortisone limit the severity and extent of infarction 24 hours after coronary artery occlusion in dogs Several possibilities were proposed to explain the infarct reducing effect, including coronary vasodilatation, increased myocardial contractility, and stabilization of myocardial cell membranes. Spath and associates[24] showed that pre or post treatment of cats with methylprednisolone prevented the decline in CPK and lysosomal hydrolase activity of ischemic myocardium, indicating that lysosomal disruption is a consequence of myocardial ischemia and that pre or posttreatment with methylprednisolone prevents the leakage of myocardial lysosomal and cellular enzymes responsible for autolytic processes

The radiocalcium uptakes were significantly decreased in dogs given hydrocortisone simultaneously with the epinephrine infusion Myocardial calcium concentrations also were significantly decreased with dipyridamole and hydrocortisone but the decrease with ASA was not

statistically significant Furthermore the histological damage when subjected to evaluation without knowledge of prior treatment was less severe in all three treatment groups than in the group infused with epinephrine alone Surprisingly there were no significant changes in serum enzyme levels (SGOT CPK) in any of the three groups when compared to the group infused with epinephrine alone The reason for this discrepancy between calcium uptakes and histologic findings vs. serum enzyme changes remains unclear but raises the question as to whether or not serum enzyme changes provide a reliable index of irreversible tissue injury

Summary

A reproducible model for producing diffuse myocardial injury (epinephrine infusion) has been developed to study the cardioprotective effects of agents or maneuvers which might alter the evolution of acute myocardial infarction Infusions of epinephrine (4 μg per kilogram per minute for 6 hours) increased radiocalcium uptakes into intact myocardium and each of its subcellular components with the mitochondrial fraction showing the most consistent changes when compared to saline infused control animals (4 957 vs 827 counts per minute per gram of dried tissue or fraction) Myocardial concentrations of calcium also increased significantly (12 0 vs 5 0 mg per 100 Gm of fat free dry weight) Infusions of calcium chloride sufficient to raise serum calcium concentrations 2 mEq per liter failed to increase calcium influx into the myocardial cell Mitochondrial radiocalcium uptakes were significantly decreased in animals pretreated with acetylsalicylic acid or dipyridamole or when hydrocortisone was added to the epinephrine infusion (2 682 2 803 and 3 424 counts per minute per gram of dried fraction respectively) Myocardial calcium concentrations also were decreased (11.2, 8 3 and 8 9 mg per 100 Gm of fat free dry weight respectively) in the three treatment groups, being significantly decreased only in the last two Evidence of microscopic damage was graded as less severe in the three treatment groups. Acetylsalicylic acid dipyridamole and hydrocortisone all appear to have cardioprotective effects when tested in this model

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REFERENCES

1 Iseri, L. T Alexander L. C MacCaughey R S., et al. Water and electrolyte content of cardiac and skeletal muscle in heart failure and myocardial infarction Am Heart J 43 215 1952

2 Jennings, R. B Kaltenbach, J P and Sommers, H M Cell death Electrolyte alterations in injured and dying myocardial cells, in Bajusz, E., editor Electrolytes and cardiovascular diseases, Switzerland, 1965 S Karger AG pp 192 203

3 Raab W Myocardial electrolyte derangement Crucial feature of pluricausal so called coronary heart disease Ann. N Y Acad. Sci. 147 627 1969

4 Zugibe F T Bell P Jr., Conley T., et al. Determination of myocardial alterations at autopsy in the absence of gross and microscopic changes, Arch. Pathol. 81 409 1966

5 Chipperfield B and Chipperfield J R Heart muscle magnesium potassium and zinc concentrations after sudden death from heart disease Lancet 2 293 1973

6 Jennings R. B Sommers H M Kaltenbach, J P et al. Electrolyte alterations in acute myocardial ischemic injury Circ Res. 14 260 1964

7 Lindeman R. D Yunice, A. A., Baxter D J., et al. Myocardial zinc metabolism in experimental myocardial infarction, J Lab Clin Med 81 194 1973

8 Yunice A. A. Baxter D J Kraikitpanitch S., et al Myocardial calcium in experimental myocardial infarction Cardiology 59 387 1974

9 Herdson P. B Sommers H M and Jennings, R. B A comparative study of the fine structure of normal and ischemic dog myocardium with special reference to early changes following temporary occlusion of a coronary artery Am J Pathol. 46 367 1965

10 Jennings, R. B Sommers, H M Herdson, P B et al. Ischemic injury of myocardium Ann N Y Acad Sci. 156 61 1969

11 Jennings R B and Shen A C Calcium in experimental myocardial ischemia in Bajusz E and Rona G editors Myocardiology Recent advances in studies on cardiac structure and metabolism Baltimore 1972, University Park Press pp 639 655

12 Handforth C P Isoproterenol induced myocardial infarction in animals, Arch. Pathol 73 161 1962.

13 Maruffo C S Fine structural study of myocardial changes induced by isoproterenol in rhesus monkeys Am J Pathol 50 27 1967

14 Bloom S and Cancilla P A. Myocytolysis and mitochondrial calcification in rat myocardium after isoproterenol, Am. J Pathol. 54 37 1969

15 Szakacs J E and Mehlman B Pathologic changes induced by l norepinephrine Am J Cardiol. 5 619 1960

16 Maling, H. M Highman B and Thompson E C Some similar effects after large doses of catecholamines and myocardial infarction in dogs, Am J Cardiol 5 628 1960

17 Ferrans V J Hibbs, R G Black, W C., et al Isoproterenol induced myocardial necrosis Am Heart J 68 71 1964

18 Wexler B C Judd, J T and Kittinger G W Myocardial necrosis induced by isoproterenol in rats Angiology 19 665 1968

19 Ostadal B Rychterova, V., and Poupa O Isoproterenol induced acute experimental cardiac necrosis in the turtle (Testudo horsfiedli) Am. Heart J 76 645 1968

20 Bloom S and Davis D L Calcium as mediator of isoproterenol induced myocardial necrosis Am J Pathol 69 459 1972
21 Haft J I Gershengorn K Kranz P D et al Protection against epinephrine induced myocardial necrosis by drugs that inhibit platelet aggregation Am J Cardiol 30 838 1972
22 Johnson A S Schayel R Sheinberg S R et al Effect of cortisone in the size of experimentally produced infarcts Circulation 7 224 1953
23 Libby P Maroko P R Bloor C M et al Reduction of experimental myocardial infarct size by corticosteroid administration J Clin Invest 52 599 1973
24 Spath J A Jr Lane D L and Lefer A M Protective action of methylprednisolone on the myocardium during experimental myocardial ischemia in the cat Circ Res 35 44 1974
25 Shen A C and Jennings R B Myocardial calcium and magnesium in acute ischemic injury Am J Pathol 67 417 1972
26 Shen A C and Jennings R B Kinetics of calcium accumulation in acute myocardial ischemic injury Am J Pathol 67 441 1972
27 Fleckenstein A Specific inhibitors and promotors of calcium action in the excitation contraction coupling of heart muscle and their role the prevention and production of myocardial lesions *in* Harris P and Opie, L H editors Calcium and the heart New York, 19 1 Academic Press Inc pp 135 188
28 Shell W E Kjekshus, J K and Sobel B E Quantitative assessment of the extent of myocardial infarction in the conscious dogs by means of analysis of serial changes in serum creatine phosphokinase activity J Clin Invest 50 2614 1971
29 Shell W E Lavelle J F Covell J W et al Early estimation of myocardial damage in conscious dogs and patients with evolving acute myocardial infarction, J Clin Invest 52 2579 1973

His bundle recordings in a case of complete atrioventricular block combined with pre-excitation syndrome

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Ventricular pre-excitation associated with high degree atrioventricular (A-V) block is a rare condition. Few cases of spontaneous A-V block in combination with a Wolff-Parkinson-White (WPW) syndrome have been reported in the literature.[3] In addition, there have been some observations on constant or transient A-V block in patients with WPW syndrome after accidental or intentional surgical interruption of the normal A-V bridge. In six cases with this combination the findings in the surface electrocardiogram (ECG) have been confirmed by His bundle recordings. This report describes a patient with complete A-V block within the nodal system and intermittent conduction through an accessory pathway proved by His bundle electrography.

Case report

This 49-year-old male patient attended the clinic because of attacks of dizziness. A slow pulse rate was observed by his physician. Despite these intermittent attacks the patient did hard physical labor up to the day of admission. Other than the present complaints the patient had a perfect health history. Tachycardias had never been observed. No former ECG recordings were available. The ECG on admission showed a complete A-V block. The sinus frequency was 62 per minute. The ventricular rate was 36 per minute. The QRS complexes were short (0.08 sec.) and of normal configuration (Fig. 1). During monitoring in the coronary care unit some extrasystoles with widened QRS complexes (0.18 sec.) were observed. Further analysis revealed that these ventricular complexes showed a delta wave and were preceded by a P wave with a P-R interval of 0.12 sec. (Fig. 2, upper tracing). This intermittent conduction occurred even without significant changes in sinus rate. There was no relationship between the preceding junctional beats and conducted P waves with short P-R interval and WPW-shaped ventricular complexes. The junctional rhythm was influenced by the conducted beats. After accelerating the sinus rhythm above 80 per minute by atropine and by exercise, one-to-one conduction was established. In this situation the ventricular complexes showed a WPW syndrome type A (Fig. 2, bottom tracing).

For further analysis His bundle electrography was performed according to the method of Scherlag and associates. For atrial and ventricular stimulation a modified Medtronic pacemaker (Model 5837) was used. The ECG (Leads I to III), His bundle electrogram (HBE), and lower right atrial electrogram (RAE) were simultaneously recorded with a six channel ECG recorder (Siemens Cardirex). During His bundle electrography the patient showed a sinus arrhythmia with a mean frequency of about 72 per minute. The P-P interval varied from 780 to 860 msec. There was a complete block within the normal A-V conduction system. The block was located at the level of the A-V node, the sinus impulses thus being blocked after the A wave in the HBE. The ventricle was activated by a junctional rhythm with a normal H-V interval (40 msec.) and small QRS complexes (80 msec.). At cycle lengths shorter than 800 msec. the atrial complex was followed by a ventricular depolarization. The conducted beats showed a widened QRS complex and a delta wave. In the HBE no His potential could be recorded between the A wave and the following V wave. The interval between the A wave in the HBE and the beginning of the delta wave in the ECG was 120 msec. (Fig. 3, left side). These beats were therefore assumed to be conducted through an accessory pathway bypassing the normal A-V conducting system. During high rate atrial stimulation a one-to-one conduction through the accessory pathway was observed at pacing rates from 75 to 155 per minute (Fig. 3, right side). At a pacing rate of 140 to 155 per minute the first atrial impulses were still conducted through the accessory pathway. Some seconds later the impulses were completely blocked at the same pacing rate (Fig. 4). At a basic cycle length of 700 msec. the effective refractory period (ERP) of the accessory pathway was 380 msec.

During high rate and programmed single stimulation of the

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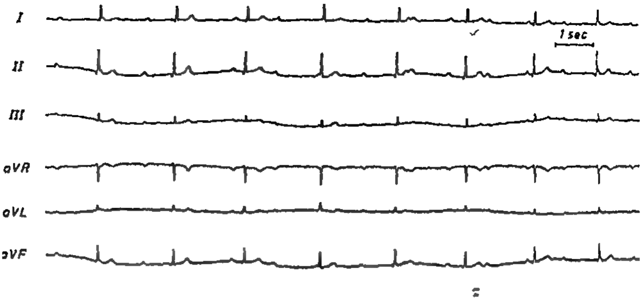


Fig 1 ECG (Leads I to III aV$_R$ aV$_L$ aV$_F$) of the patient at admittance Sinus rate 62 per minute with complete A V block The ventricle is activated by a junctional rhythm with a frequency of 36 per minute

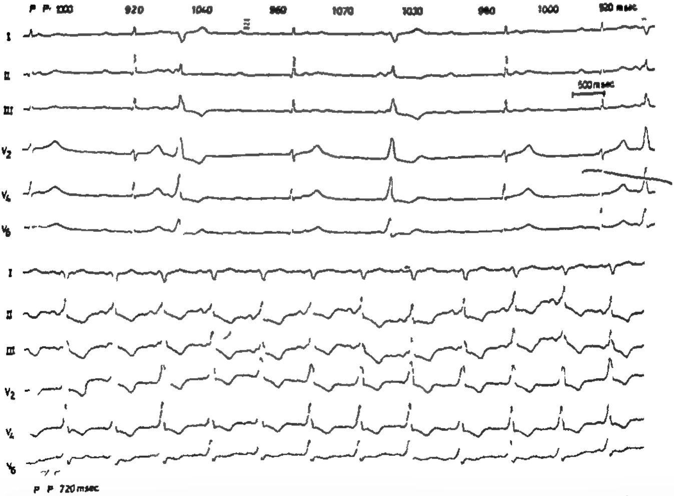


Fig 2 ECG (Leads I to III, V$_2$ V V) of the same patient during rest (top) and after exercise (bottom) some hours later The sinus rate at rest is about 60 per minute (cycle length between 920 and 1070 msec) with A V block and a slow junctional rhythm (QRS 0 08 sec) P waves are intermittently conducted with short P R interval (0 12 sec.) and widened ventricular complexes (QRS 0 18 sec) showing a delta wave There is no correlation between conduction through the accessory pathway and the P P interval or the preceding junctional beats After exercise heart rate is accelerated to 83 per minute (cycle length 720 msec) At this frequency a one to one conduction is registered with short P R intervals (0 12 sec) and WPW type A shaped ventricular complexes

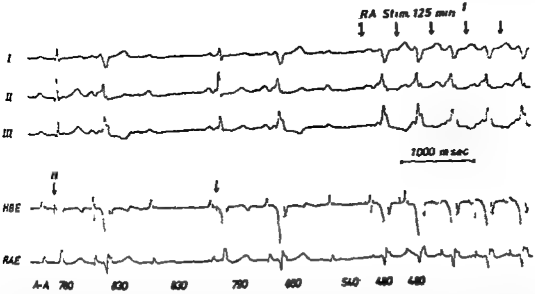


Fig 3 ECG (Leads I to III) His bundle electrogram (HBE) and low right atrial electrogram (RAE) of the same patient during sinus rhythm and atrial stimulation At sinus rhythm the P P intervals are not constant Sinus beats with a cycle length above 800 msec are blocked after the A wave Sinus beats with a cycle length below 800 msec. are conducted through an accessory pathway In addition the ventricle is activated by a slow junctional rhythm (*H* arrow) with a H V interval of 40 msec (left side) With the onset of atrial stimulation (125 per minute) one-to-one conduction through an accessory pathway occurs No His potential can be recorded between the A waves and the conducted WPW shaped ventricular complexes (right side)

right ventricle (RV) no retrograde ventriculoatrial (V A) conduction could be observed—neither at any pacing rate nor stimulus prematurity

After atropine (0 02 mg. per kilogram intravenously) the sinus rate was enhanced to 98 per minute with a one to one conduction through the accessory pathway (Figs 5 and 6) In this situation programmed atrial stimulation was performed After a stimulus-induced premature atrial beat the postextrasystolic pause up to the next spontaneous P wave was prolonged (30 msec) in comparison to the basic cycle length (668 msec) The P wave of the return cycle was not conducted to the ventricle Later the P P interval shortened again and a one-to-one conduction through the accessory pathway was reestablished (Fig 5) During premature ventricular stimulation no retrograde V A conduction was registered and therefore the P P intervals remained unchanged In spite of this, the next P waves after the stimulus-induced ventricular complex were completely blocked Then a one to one conduction through the accessory pathway reoccurred (Fig 6)

Neither during the control period nor after application of atropine were we able to demonstrate any A V conduction through the normal nodal His Purkinje system

The implantation of a ventricular demand pacemaker was decided. Three months later the patient was examined in the pacemaker clinic He was free of symptoms and back at work After blocking the pacemaker by external chest stimulation the ECG showed again a complete A V block with a slow junctional rhythm

Discussion

Since the first description of bundle branch block with short P R interval by Wolff Parkinson and White[4] there have been only some reports on the association of this syndrome with high degree A V block This combination was observed in patients with coronary heart disease or rheumatic carditis [1] and in a victim of an accident In addition a constant or transient A V block has been registered after planned surgical interruption of the normal A V bridge in patients with WPW syndrome and intractable tachycardias Timmis and associates described a case of pre excitation syndrome in combination with a second degree A V block appearing after surgical correction of a ventricular septal defect Conduction through the accessory pathway occurred only if the P waves appeared at the end of the T wave of the preceding normal ventricular complex This phenomenon could be explained by retrograde concealed conduction into the bypass after ventricular depolarization through the normal nodal system Other authors observed combined conduction disturbances in the normal and accessory pathway during spontaneous atrial tachycardia or during high rate atrial pacing

In two cases of WPW syndrome terminating in a complete A V block histological examination revealed accessory tracts in addition to the

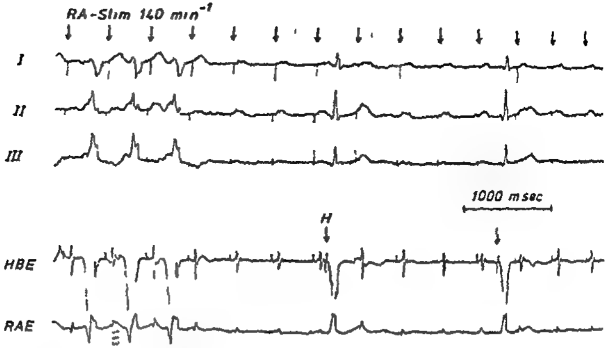


Fig 4 Fatigue of the accessory pathway during high rate atrial stimulation First the atrial impulses were conducted one to one through the bypass (left side) Later a complete block occurs at the same pacing rate and the ventricle is activated by a slow junctional rhythm (*H* arrow)

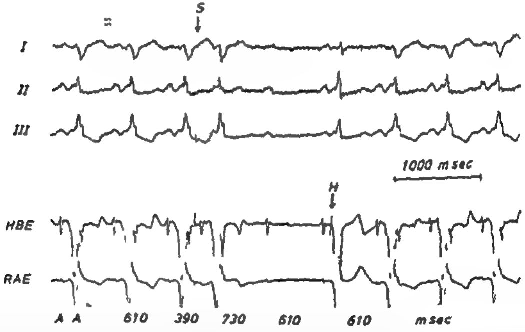


Fig 5 ECG and His bundle recordings in the same patient after application of atropine The cycle length is shortened up to 610 msec and the P waves are conducted one to one through an accessory pathway after a stimulus induced premature atrial beat (S arrow) the return cycle is prolonged up to 730 msec and this P wave is blocked The cycle length then shortens again The next ventricular complex is a fusion beat between a conducted impulse through the accessory pathway and a junctional escape beat After this one to one conduction is re-established through the bypass

normal A V conduction system both involved in ischemic alterations Levine and Burge[2] found an accessory Kent bundle bypassing the A-V node whereas Lev and associates[1] described James and Mahaim fibers adjacent to the normal conduction system

Massumi[14] studied a case of second degree Typ II block in the presence of WPW syndrome with the aid of His bundle recordings There was bilateral bundle branch block within the norma A V conduction system Explanation of intermit tent antegrade conduction through the bypa

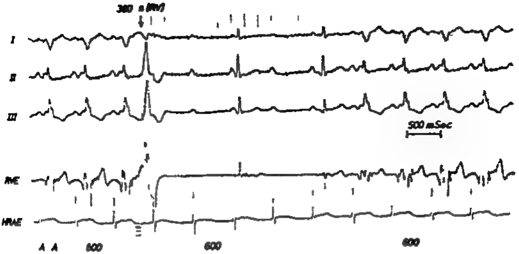


Fig 6 (Leads I to III) right ventricular electrogram (RVE) and high right atrial electrogram (HRAE) of the same patient after application of atropine during programmed right ventricular stimulation At a cycle length of 600 msec. there is one to-one conduction through the accessory pathway The four sinus beats following a stimulus-induced premature ventricular beat (S VR) with a coupling interval of 380 msec are blocked in spite of the fact that cycle length did not change (no retrograde V A conduction)

assumed supramaximal conductivity Despite intermittent antegrade block within the normal and accessory pathway a one to one retrograde V A conduction during ventricular stimulation was observed Coumel and associates [9] described four patients with WPW syndrome and higher degree A V block who were examined by His bundle electrography In two patients with congenital A V block the level of the block within the normal conduction system was above the bundle of His. In the other two cases one with a surgically induced block and one of ischemic origin the block was located within the His Purkinje system. By the electrophysiological studies the pre-excitation pathway was characterized as a bundle of Kent type in two cases and a James Mahaim type in one case In the fourth patient these two possibilities were discussed Bensaid and associates studied a case of Duchenne s muscular dystrophy with a high degree A V block and WPW syndrome by His bundle recordings There was a trifascicular block within the normal pathway The discussion suggested that the accessory pathway was a Kent bundle or James Mahaim fibers

In the case reported here there was a complete block within the normal A V conduction system Impulse conduction through the normal nodal system could be observed neither during exercise nor after application of atropine His bundle study indicated the level of block to be above the bundle of His The ventricle was activated by a slow junctional rhythm with a normal H V interval The etiology of this block was unknown the patient having a history of perfect health The clinical examination showed no abnormalities Theoretically this type of block could be of congenital origin however no ECG recordings prior to the admission of the patient were available for comparison

The nature of pre excitation could be best explained by a left sided Kent bundle bypassing the nodal system During phases of one to one conduction the patient showed a typical WPW syndrome type A with a P delta interval of 0 12 sec In the His bundle electrogram no His potential could be recorded between the A wave and the conducted ventricular complexes of pre excitation type During atrial stimulation a rate dependent block within the accessory pathway was documented Conduction through the bypass occurred at cycle lengths between 800 and 380 msec At shorter or longer cycle lengths the bypass was blocked The interval between the A wave and the delta wave was constant up to block without any change of QRS configuration at shorter coupling intervals The fact that accessory pathway conduction occurred only at a small range of cycle lengths was observed in other patients with WPW syndrome without spontaneous A V block This zone of accessory pathway conduction was sandwiched by zones of exclusive normal A V conduction [30-33] This was thought to occur by phase 3 and phase-4 block of the acces

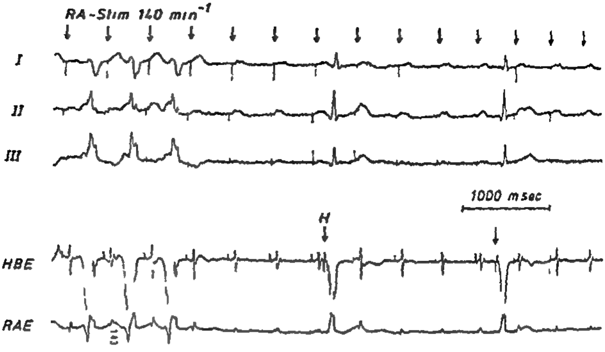
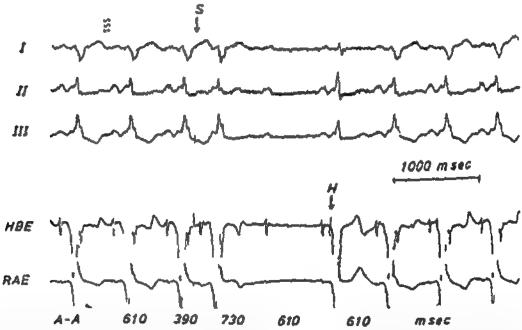


Fig 4 Fatigue of the accessory pathway during high rate atrial stimulation First the atrial impulses were conducted one to one through the bypass (left side) Later a complete block occurs at the same pacing rate and the ventricle is activated by a slow junctional rhythm (*H* arrow)



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conduction through the anomalous bypass Circulation 34 ,34 1966

Timmis, G C Henke J Gordon S and Ramos R G *The Wolff Parkinson White syndrome in advanced* atrioventricular block Am J Cardiol 28 592 1971

Dreifus, L S Nicholas, N Morse D Watanabe Y and Truex, P Cont ol of recurrent tachycardia of Wolff *Parkinson White syndrome by surgical ligature of the* A V bundle Circulation 38 1030 1968

Edmonds, J H Ellison R G and Crew T L Surgically induced atrioventricular block as treatment *for recurrent atrial tachycardia in* Wolff Parkinson White syndrome Circulation 39(*Suppl* 1) 105 1969

Dunaway M C King, S B Hatcher C R and Logue R B Disabling supraventricular tachycardia of Wolff Parkinson White syndrome (Type A) controlled by surgical A V block and demand pacemaker *after epicar*dial mappin studies Circulation 45 5?? 1972

Massumi, R A His bundle recordings in bilateral bundle branch block *combined with Wolff Parkinson* White syndrome *Circulation* 42 287 1970

Coumel, P Gourgon, R Slama R and Bouvrain Y Conduction auriculoventriculaire pardes fibres de pre excitation, associée à un bloc complet de la voie nodo hisienne *Etude électrocardiographique* de quatre cas Arch mal Coeur 66 85 19/3

Bensaid, J Marsaud G Monassier J P and Blanc C *Bloc* auriculo entriculaire de haut degré associé à un syndrome de *Wolff* Parkinson White au cours d une myopathie de type Duchenne de Boulogne Ann Cardiol Angeiol 24 67 19/5

Scherlag B J Lau S H Helfant R H Berkowitz W D *Stein E and* Damato A N Catheter technique for recording His bundle *activity in man* Circulation 39 13 1969

Wolff L Parkinson J and White P D Bundle branch block with short P R interval in healthy young people prone to paroxysmal *tachycardia*, AM HEART J 5 685 1930

Castellanos A Jr Chapunoff E Castillo C Mayting O and Lemberg L His bundle electrograms in two cases of Wolff Parkinson White *(pre excitation)* syndrome Circulation 41 399 1970

Narula O S Wolff Parkinson White syndrome A review *Circulation 47* 872, 1973

Roelandt J Schamroth L *Draulans J and* Hugenholtz, P G Functional characteristics of the Wolff Parkinson White bypass A study of six patients with His bundle electrograms AM HEART J 85 260 1973

26 Wellens H J J *and Durrer D Combined conduction* disturbances in two A V pathways in patients with the Wolff Parkinson White syndrome Eur J Cardiol 1 23 1973

27 Wellens H J J *Contribution of cardiac pacing to our* understanding of the Wolff Parkinson White syndrome Br Heart J 37 231 1975

28 Segers, M Lequime J and Denolin H L activation ventriculaire précoce de certains coeurs hyperexcitables *Etude de l onde Δ de l electrocardiogramme* Cardiologia (Basel) 8 113 1944

29 Pick A and Katz L N Disturbances of impulse formation and conduction in the pre-excitation (WPW) syndrome *Their bearing on its mechanism* Am J Med 19 759 1955

30 Lau S H Stein E Kosowsky B D Haft J I Lister J and Damato A N Atrial pacing and atrioventricular *conduction in anomalous atrioventricular excitation* (Wolff Parkinson White *syndrome)* Am J Cardiol 19 354 1967

31 Durrer D Schuilenburg R M and Wellens H J J Pre excitation revisited, Am J Cardiol 25 690 1970

32 *Massumi R A and Vera, Z Patterns* and mechanisms of QRS normalization in patients with Wolff Parkinson White syndrome Am J Cardiol 28 541 1971

33 Coumel P Waynberger M Fabiato A Slama R *Aigueperse J and Bouvrain* Y Wolff Parkinson White syndrome Problems in evaluation of multiple accessory pathways and surgical therapy Circulation 45 1216 1972

34 Posen K M *Lopez Arostegui F and Pouget J M* Pre excitation with normal PR intervals A case secondary to low Kent bundle conduction Chest 62 581 1972

35 *Castellanos A Castillo C A* Agha A S Befeler B and Myerburg, R J Functional *properties* of accessory AV pathways during premature atrial stimulation Br Heart J 35 578 1973

36 Zipes D P DeJoseph R L and Rothbaum D A Unusual properties of *accessory pathways Circulation* 49 1200 1974

37 Neuss H Nowak F and Schlepper M Changes of conduction properties of anomalous pathways in cases with W P W *syndrome Z Kardiol* 62 459 1973

sory pathway or by acceptance of supernormal conduction[10,33] However during monitoring we observed conducted WPW beats outside the range of cycle length measured during atrial stimulation In Fig 2 a P wave at a cycle length of 1 070 msec was conducted through the accessory pathway Perhaps retrograde concealed conduction of the junctional impulses into the bypass influenced antegrade conduction via Kent bundle, as described by others[13,14,35] On the other hand after application of atropine a sinus beat occurring 730 msec after a premature atrial stimulus was blocked (Fig 5) During control stimulation a one to one conduction was observed at this cycle length We have no explanation for these findings

Roelandt and associates stated that rate dependent complete block within the bypass cannot be due to a true increase in refractoriness but must be due to interference at the ventricular level We were able to demonstrate such interference during ventricular pacing After enhancing the sinus rate by atropine and establishing a one to one antegrade conduction through the bypass a premature ventricular stimulus led to a complete antegrade block of the accessory pathway for some beats in spite of the fact that the sinus frequency did not change (Fig 6) Retrograde V A conduction could never be documented

In addition to the bradycardia and tachycardia dependent block within the accessory pathway a fatigue of the Kent bundle conduction could be observed During a longer period of atrial stimulation at a critical rate the impulse was first conducted one to one and later completely blocked (Fig 4) Perhaps this phenomenon is to be explained by incomplete recovery of the accessory pathway during stimulation at critical rates[37]

The findings reported here support the thesis of at least two functionally different A V pathways in patients with pre excitation syndrome In this case the normal nodal pathway was completely blocked whereas the anomalous bypass allowed antegrade A V conduction only within a small range of cycle length However some observations on anomalous pathway conduction in this patient remain unexplained

Summary

In a patient with complete A V block suffering from attacks of dizziness an intermittent A V conduction with a short P R interval and a delta wave of the conducted ventricular complex were observed After accelerating the sinus rate by atropine and by exercise, one to one conduction was established with QRS complexes of WPW type A configuration His bundle recording revealed a complete block within the normal conduction system at the level of the A V node A slow junctional rhythm with a normal H V interval was activating the ventricle During atrial pacing a one to one conduction through an accessory pathway could be documented at cycle lengths between 600 and 380 msec sandwiched in between zones of complete block at smaller or longer cycle lengths During ventricular stimulation no retrograde V A conduction could be observed The findings support the thesis of at least two functionally different A V pathways in patients with pre excitation syndrome

REFERENCES

1 Feldmann H and Koch E Zum Syndrom der Verbreiterung der QRS Gruppe auf Kosten von P Q Z Kreislaufforsch 35 512 1943

2 Levine H D and Burge J C Septal infarction with complete heart block and intermittent anomalous atrioventricular excitation Histological demonstration of a right lateral bundle Am Heart J 36 431 1948

3 Rodstein M A case of anomalous auriculoventricular conduction with auriculoventricular block and a history of rheumatic fever N Y J Med 51 789 1951

4 Fox T T Weaver J and March H W On the mechanism of the arrhythmias in aberrant atrioventricular conduction (Wolff Parkinson White) Am Heart J 43 507 1952

5 Scherf D Blumfeld S and Mueller P A V conduction disturbance in the presence of the pre excitation syndrome Am Heart J 43 829 1952

6 Hoffman I Morris H M Friedfeld L and Gitler R Aberrant beats of Wolff Parkinson White configuration in arteriosclerotic heart disease Br Heart J 18 301 1956

7 Zuckermann R Ein Fall von Wolff Parkinson White Z Kreislaufforsch 45 712 1956

8 Fox T T Further remarks on the syndrome of aberrant A V conduction (Wolff Parkinson White) Am Heart J 53 771 1957

9 Le Damany L and Gouffalt J Syndrome de Wolff Parkinson et White acquis au cours d une pousee de rheumatisme cardiaque Arch Mal Coeur 51 954 1958

10 Moret P R Schwartz M L and White T J The Wolff Parkinson White syndrome and second degree heart block Report of a case and a discussion of the significance of the association of these phenomena. Cardiologia (Basel) 34 43 1959

11 Wolff L Anomalous atrioventricular excitation (Wolff Parkinson White syndrome) Circulation 19 14 1959

12 Lev M Leffler W B Langendorf R and Pick A Anatomic findings in a case of ventricular pre excitation (WPW) terminating in complete atrioventricular block. Circulation 34 718 1966

13 McHenry P L Knoebel S B and Fisch C The Wolff Parkinson White (WPW) syndrome with supernormal

Fig 1 Posteroanterior (A) and lateral (B) roentgenogram of chest taken on admission demonstrating opened lower sternotomy wire pointing posteriorly

Beck features a falling arterial pressure a rising venous pressure and a small quiet heart This description evolved primarily from a surgeon s exposure to acute rapidly progressing cardiac tamponade that resulted from traumatic stab or gunshot wounds When cardiac tamponade evolves more slowly the clinical signs may be subtle With the elucidation of the pathophysiologic events underlying cardiac tamponade the physician can now more effectively discriminate the signs of cardiac tamponade from constrictive pericarditis or restrictive cardiomyopathy The patient presented here nevertheless had classic signs of acute cardiac tamponade

The evaluation of the patient with suspected pericardial effusion should be accomplished by the selective use of a number of available procedures Roentgenographic evaluation may show increased heart size usually without pulmonary vascular prominence In addition displacement of the epicardial fat line within the cardiac silhouette can be pathognomonic for pericardial effusion. In this patient these findings were not apparent but the detection of the opened posteriorly pointing wire suture that was noted on the routine chest roentgenogram was of critical importance While angiography and intravenous

Table I Causes of acute hemopericardium

A Nontraumatic	B Traumatic
1 Acute myocardial infarction	1 Cardiac or pulmonary surgery
2 Rupture of aortic aneurysm	2 Cardiac catheterization
3 Neoplasm	3 Intravenous catheters
4 Blood dyscrasias	4 Foreign body penetration
5 Acute rheumatic fever	5 Blunt chest injury
6 Idiopathic pericarditis	
Uremia	
8 Infectious pericarditis	
9 Collagen vascular disease	
10 Irradiation	
11 Anticoagulation	

carbon dioxide injection may be of use these procedures are time consuming and potentially dangerous in the emergent situation [9] Echocardiography was first reported to be of use in the diagnosis of pericardial effusion in 1965 It is now well established in clinical use and indeed is the most expeditious method of diagnosis A more recent study comparing pericardial fluid removed at surgery with echocardiographic evidence of effusion has documented not only the

Spontaneous cardiac tamponade due to sternotomy wire suture

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Spontaneous pericardial tamponade is most frequently due to neoplastic invasion idiopathic or infectious pericarditis and uremia Both penetrating and nonpenetrating trauma are also well recognized causes of cardiac tamponade[1] Iatrogenic causes of traumatic tamponade are assuming increasing importance based on reports documenting associations with central venous catheters cardiac catheterization and following cardiac surgery[2-4] This report is the first documentation of cardiac tamponade caused by wire suture routinely used in sternotomy closure In view of the increasing number of cardiac surgical procedures an estimated 30 000 annually for coronary bypass alone this potential postoperative complication is notable

Case report

A 16 year old boy was admitted to Barnes Hospital on Dec 7 1974 for evaluation of chest pain He was previously hospitalized in August 1973 for cosmetic repair of a pectus excavatum deformity At the final admission he presented with complaints of sudden onset of severe sharp midsternal pain with radiation to both shoulders and minimal dyspnea He denied trauma to the chest and denied taking any medication

Physical examination revealed a temperature of 38 C a blood pressure of 120/80 mm Hg with no paradoxical pulse and a pulse of 85 per minute Jugular venous pulses were not elevated The lungs were clear to auscultation and percussion A pectus deformity and a longitudinal scar were noted over the sternum Cardiovascular examination revealed an increased pulmonic second sound and a two component pericardial friction rub

The chest roentgenogram (Fig 1) revealed evidence of the prior median sternotomy with two wire sutures in place Though not initially appreciated the lower wire suture was open with the tip pointing posteriorly The cardiac silhouette was enlarged and there was minimal pulmonary redistribution The electrocardiogram (ECG) revealed an incomplete right bundle branch block that was present on the previous hospitalization additionally marked ST elevation not evident on prior ECG was noted in the lateral leads The hemoglobin was 14 4 Gm per 100 ml and the white blood count was 8 700 per square centimeter with normal differential count Arterial blood gases SMA 12, sedimentation rate and urinalysis were normal

During the first hospital day the patient noted diminution of the chest pain and the two component rub disappeared Approximately 24 hours after admission the chest pain recurred suddenly with an accompanying severe epigastric pain Physical examination at this time revealed an acutely ill male patient who had a blood pressure of 86/70 mm Hg with 16 mm Hg paradox a pulse of 130 per minute and a respiratory rate of 26 per minute There was jugular venous distention but Kussmaul's sign was not observed The lungs were clear to auscultation Heart sounds were distant and the two component pericardial rub was no longer audible Examination of the abdomen revealed only tenderness to palpation and a slightly enlarged liver The femoral pulses were minimally palpable during inspiration

A central venous catheter was inserted and a pressure of 2[illegible] cm H O was recorded Intravenous fluids and isoproterenol were administered and the blood pressure increased to 100/[illegible] mm Hg A repeat chest roentgenogram and ECG were unchanged An emergency pericardiocentesis was performed and 30 ml of bloody fluid with a hematocrit of 45 per cent was withdrawn The bloody fluid did not clot at 10 minutes An echocardiogram (Fig 2 A) revealed definite evidence of pericardial effusion The patient was taken immediately to the operating room and an emergency thoracotomy was done under general anesthesia The pericardium was opened, and approximately 500 ml of blood were removed Inserting a hand into the pericardium the surgeon detected a wire protruding into the heart The site of penetration was tamponaded with a finger and the wire removed When exposed the right ventricle revealed multiple abrasions but no further bleeding sites The patient tolerated the procedure well and had an uncomplicated postoperative course Si[illegible] months following discharge he was in good health

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Discussion

Clinical presentation and evaluation The classical clinical description of cardiac tamponade by

iate though we advise against the routine use of either of these procedures Ear densitometry after indocyanine green injection has also been proposed but this requires special equipment

Etiology of pericardial tamponade The etiology of acute tamponade is most often infectious neoplastic or uremic disease [9] Other medical causes include collagen vascular disease acute rheumatic fever myocardial infarction and anticoagulation. However with earlier diagnosis and improved therapeutic approaches to uremia neoplasm and acute rheumatic fever cardiac tamponade associated with these causes is now seen less frequently Traumatic causes of cardiac tamponade have been recognized for some time and there are recent reviews of experience with penetrating wounds of the heart Recent reports documenting acute cardiac tamponade secondary to central venous catheters cardiac catheterizaiton and cardiac surgery emphasize the increasing importance of iatrogenic causes of traumatic tamponade [1, 3] Table I summarizes the etiologies that are most commonly associated with acute tamponade and hemopericardium In addition to the etiologies noted in Table I this report represents the first notation of cardiac tamponade due to penetration by a sternotomy wire suture

Summary

The first case of spontaneous cardiac tamponade caused by wire suture for sternotomy closure is presented The proper analysis of bloody pericardial fluid including simultaneous aspirate and venous hematocrit oxygen content and coagulation studies is emphasized In addition the causes of acute hemopericardium are reviewed Spontaneous cardiac tamponade as a potential late complication of cardiac surgery should be considered in the postoperative patient who presents with pericarditis or a sudden change in cardiac status

REFERENCES

1. Jones, E W and Helmsworth J Penetrating wounds of the heart thirty years experience Arch. Surg 96 671 1968
2. Shoemaker W Carey J S Yao S T Mohr P A Amato J J Printen K J Corley R D Manson D O Yousset J and Shoemaker N J Hemodynamic alterations in acute cardiac tamponade after penetrating injuries of the heart Surgery 67 754 1970
3. Stein L, Shubin H and Weil M M Recognition and management of pericardial tamponade J A M A 225 503 1973
4. Dane T E B and King E E Fatal cardiac tamponade and other mechanical complications of central venous catheters Br J Surg 62 6 1975
5. Mundth, E D and Austen G W Surgical measures for coronary heart disease N Engl J Med 293 124 1975
6. Beck C S Two cardiac compression triads, J A M A 104 714 1935
7. Shabetai R Fowler N O and Guntheroth, W G The hemodynamics of cardiac tamponade and constrictive pericarditis, Am J Cardiol 26 480 1970
8. Burch G E and Phillips, J H Methods in the diagnostic differentiation of myocardial dilatation from pericardial effusion Am Heart J 64 266 1962
9. Baron M G Pericardial effusion Circulation 44 294 1971
10. Moraski R E Sandler I A O Hern J A, and Bonskaros G Evaluation of right atriography for the detection of pericardial effusion Am J Med Sci. 256 360 1968
11. Clark R L Mildram J W and Yawn D H Fatal aortic perforation and cardiac tamponade due to a Kirschner wire migrating from the right sternoclavicular joint South Med J 67 316 1974
12. Feigenbaum H Echocardiographic diagnosis of pericardial effusion Am J Cardiol. 26 4 5 1970
13. Horowitz M S Schultz, C S., Stinson E B Harrison D C and Popp R L Sensitivity and specificity of echocardiographic diagnosis of pericardial effusion, Circulation 50 239 19 4
14. Bishop L H Jr Estes E M Jr and McIntosh H D The ECG as a safeguard in pericardiocentesis J A. M A. 162 264 1956
15. Sobol J M Thomas, H M Jr and Evans R W Myocardial laceration not demonstrated during pericardiocentesis N Engl J Med 292 1222 1975
16. Shabetai R Fowler N O and Fenton J C Restrictive cardiac disease pericarditis and the myocardiopathies, Am Heart J 69 2 1 1965
17. Wood P C Observations on pericardial disease Med Clin North Am 37 1639 1953
18. Mills C W Simple clinical aid in diagnosis of hemorrhagic pericardiac effusion J A M A 150 1208 1952
19. Stone J R and Martin R H Bloody pericardial fluid or intracardiac blood? Ann Intern Med 77 592 1972
20. Lajos T Z Black H E Cooper R G and Wanka J Pericardial decompression Ann. Thorac Surg 19 47 19 5
21. Fowler N O Pericardial disease in Hurst J W editor The heart ed 3 New York 1974 McGraw Hill Book Company Inc
22. Friedberg C K Acute pericarditis, in Friedberg C K., editor Diseases of the heart ed 3 Philadelphia 1966 W B Saunders Company
23. Sugg W L Rea W J Ecker R R Webb W R Rose E F and Shaw R R Penetrating wounds of the heart J Thorac Cardiovasc Surg 56 531 1968
24. Cortes F M The pericardium and its disorders Springfield Ill 1971 Charles C Thomas, Publisher

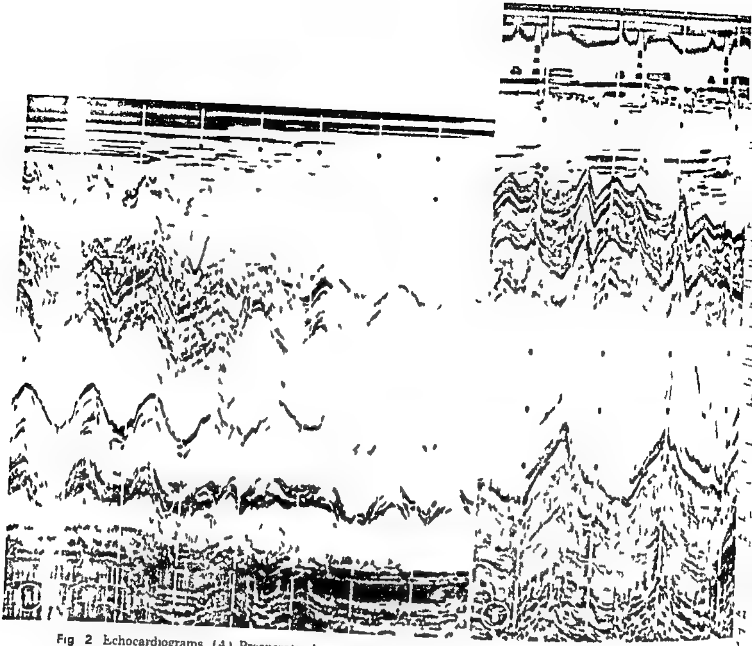

Fig 2 Echocardiograms (*A*) Preoperatively revealing a large echo free space posterior to the left ventricle consistent with a pericardial effusion and a small left ventricular dimension (*B*) Postoperatively revealing the absence of pericardial effusion

specificity but also the sensitivity of this method[1]

Analysis of pericardial fluid When grossly bloody fluid is aspirated during attempted pericardiocentesis the source may be pericardial or intracardiac The technique of continuous ECG monitoring with the paracentesis needle as an exploring electrode is one attempt to obviate penetration of the heart[11] It is known, however that ECG ST segment changes may not appear and, consequently, myocardial laceration may occur even with strict adherence to this technique[1] Of particular importance, then is proper analysis of the bloody aspirate to differentiate pericardial from intramyocardial origin The routinely advised tests are (1) simultaneous aspirate and venous hematocrits and (2) inspection of fluid for clot formation as pericardial fluid tends to be defibrinated and does not readily clot Additionally we recommend obtaining simultaneous PO_2 measurements from the aspirate and venous blood It is of interest that the hematocrit of the pericardial aspirate of this patient was equal to that of the venous sample indicating the acuteness of the tamponade due to the right ventricular lacerations Other measurements for evaluation of the bloody aspirate include injection of sodium dehydrocholate or calcium gluco

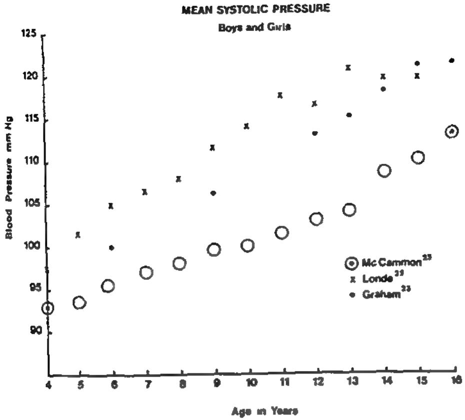

Fig 1 Mean systolic blood pressures from three separate studies (boys and girls)

There is general agreement that the systolic pressure is recorded at the point the first sound (first phase of Korotkov) [9] is heard There is less than general agreement concerning the proper determination of diastolic pressure Moss and Adams have stated that diastolic blood pressure readings when measured by the auscultatory method can be highly inaccurate In most of the series in which blood pressures were recorded on large numbers of children [4] the diastolic pressure was registered at the point of disappearance of all sound When this was not possible the point of muffling of the sound (fourth phase of Korotkov) was used The point of muffling has been shown to be up to 7 to 10 mm Hg higher than the actual diastolic pressure [4] Thus it is advisable to follow whenever possible the recommendations of the American Heart Association that the point of the muffling of the sound (fourth phase) and the disappearance of the sound (fifth phase) both be recorded

Anyone who has attempted to take the blood pressure of a small infant with the use of a mercury manometer and a stethoscope has experienced the frustrations of examining a crying infant and the lack of patient cooperation All of these factors have made the recording of an accurate blood pressure difficult in a small infant This has led to other methods such as the flush technique This method has been studied in depth by several observers [3] and will not be discussed in detail in this review The flush method represents only a close estimation of systolic pressure and often takes two observers to record the pressure but until recently it was the only method clinically feasible in neonates and small infants

There has been recent interest in measuring blood pressure in infants with the Doppler ultrasound method The details of the principles involved in the Doppler ultrasound technique have been adequately discussed in several recent articles [3] One of the drawbacks with the mercury sphygmomanometer is that the arterial wall of a small infant is often unable to generate enough sound to be heard by a stethoscope The Doppler method overcomes this The main disadvantage to its being commonly used is its cost but

Hypertension in childhood A review

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One of the many great controversies in the field of pediatrics concerns arterial hypertension in children These controversies have revolved around the definition incidence, significance and etiology of hypertension in children There are views that elevated blood pressures in children range from being rare[1] and uncommon[2-4] to not uncommon[5] When an elevated blood pressure is discovered in a child there has been a tendency by physicians to discount the significance of this finding[6] often relating it to the anxiety of the child, and physicians are often lax in their approach to hypertension[8] When one considers that it is estimated that 23 million adult Americans have elevated arterial blood pressures[9] and that this group is at high risk for stroke[10] heart disease[11,12] and kidney failure it would behoove physicians to pay more attention to the finding of an elevated blood pressure in a child There had been a historic reluctance on the part of physicians to treat elevated blood pressures mainly due to the relative lack of evidence that treatment is of significance but recent evidence[13-15] has strongly suggested the efficacy of lowering elevated blood pressures in adults including those levels previously considered to be mild There is however little evidence in the literature concerning the long term implications of elevated arterial blood pressure in children In reviewing hypertension in children it becomes apparent that there are many unanswered questions mainly due to the lack of interest and research in this area When one considers the recent surge of nationwide interest in hypertension in adults and the fact that there is little known concerning the etiology and genesis of essential hypertension in adults, perhaps more time and effort should be spent investigating this condition in children

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This review will focus on (1) normal blood pressures in children and the incidence of hypertension in children (2) the epidemiology of essential hypertension in children (3) the etiology and evaluation of secondary hypertension in children and (4) the treatment of hypertension in children

Normal blood pressure in children

In any review of hypertension in children the question always arises What are normal blood pressures? The published values vary widely and often the disparities relate to cuff size the method and technique used and the varying ages of the children studied The method most commonly used in recording blood pressure levels in children is the auscultatory method with the use of the mercury sphygmomanometer and the stethoscope One of the most important factors in accurately determining blood pressure in children is the cuff size It has been shown by several observers[1-4] that an inappropriate cuff size can falsely elevate or lower arterial blood pressure readings The recommendations of the American Heart Association[16] are that for children under one year of age the appropriate cuff size 2.5 cm from 1 to 4 years 5 or 6 cm from 4 to 8 years 8 or 9 cm for arms of adults 12 cm This has two drawbacks it assumes that children 9 years of age and older should have the same cuff used as that of an adult and that all children the same age should have the same size cuff used The practice of using a given cuff size for a given age should be disbanded and the proper cuff size should be selected on an individual patient basis This author has been impressed with the necessity of using a 15 or 17.5 cm cuff in large muscular adolescents A sphygmomanometer cuff should be used which covers at least two thirds of the upper arm[5] and there is recent evidence[17] which suggests that a cuff which encircles as much of the upper arm as possible is the correct size

November 1976 Vol 92 No 5 pp 634 647

above the ninety fifth percentile should be classified as hypertensive Londe and associates[11, 2] classified children as hypertensive if their blood pressures were occasionally above the ninety fifth percentile or consistently above the ninetieth percentile for age and sex Table I summarizes the data from Londe s study This classification is by definition arbitrary for there is obviously no sharp dividing line between normal and abnormal levels of pressure for any individual child This theoretical question becomes a practical one for the practicing physician when he is faced with a child who has blood pressures that are considered to be elevated Does this child undergo a lengthy and costly hospitalization for elevation of this problem? This unfortunately is one of the many unanswered questions relating to hypertension in children Several suggestions can be made to the physician who is faced with this problem (1) proper well functioning equipment is essential (2) the child must be as calm as possible (3) the pressure may need to be recorded repeatedly at several office visits to definitely document the presence of hypertension (perhaps the pressure could be measured in the home by a parent) (4) if the child is obese or if there is a history of essential hypertension the results of an exhaustive search for an underlying cause may be unrewarding

It also remains to be determined what happens to children whose blood pressures are above the ninetieth percentile for that matter what happens to those above the seventy fifth percentile Longitudinal studies need to be done following this type of child into and through adulthood to show the prognostic significance of an elevated blood pressure in childhood North stated that Until this relationship is shown higher blood pressures must be regarded as interesting observations not as abnormalities which demand investigation diagnosis or special programming

Incidence of hypertension There is very little information available concerning the incidence of hypertension in children Loggie stated that one to two per cent or more of children have hypertension Masland and associates studied outpatients aged 12 to 22 years and found that 1 4 per cent had blood pressures greater than 140/90 on two or more examinations Oliver and associates stated that any child with a recorded blood pressure more than 15 to 20 mm Hg over the norm should be considered hypertensive but he made no mention of the incidence If the findings of Graham and associates[3] are compiled statistically it is noted that 3 to 4 per cent of children had blood pressures greater than two standard deviations above the mean In a recent study Londe found that 12 per cent of the children he studied had labile hypertension based on at least one reading greater than the ninetieth percentile for their age and sex He found that 2 3 per cent of the children had persistently elevated blood pressures greater than the ninety fifth percentile As mentioned above the designation that those children above the ninetieth percentile are hypertensive is by definition arbitrary This renders the top 10 per cent of children hypertensive There is some indication that this may in fact be justifiable Buck in a recent study evaluated a group of 5 year old children who had elevated systolic and diastolic pressures A 7 year follow up indicated that their pressures continued to be significantly elevated

Essential vs secondary hypertension It has long been held that hypertension in children is rare and of those children who are found to be hypertensive most of them will have secondary hypertension McCrory and Nash and Haggerty and associates have stated that essential hypertension is rare in children Once an elevated blood pressure is discovered the child is often subjected to a lengthy and expensive investigation mainly because of the belief that a remediable cause will be found Platt studied 64 hypertensive patients less than 40 years of age (only two patients were under 20 years of age) and found that 75 per cent had secondary hypertension and only 25 per cent had essential hypertension Still and Cottom[3] studied 55 children with hypertension and found only 5 per cent with essential hypertension The children in their study however all had diastolic blood pressures greater than 120 mm Hg and other investigators[5] [2] have shown that the higher the blood pressure the greater the likelihood that a cause will be found There have been several recent studies that have challenged the theory that essential hypertension is rare in children Singh and Page found the incidence of essential hypertension to be 36 per cent in the 22 patients they studied (ages 7 to 32 years) Ooi and associates[3] reviewed 127 patients 12 to 40 years of age with hypertension and found the incidence of essential

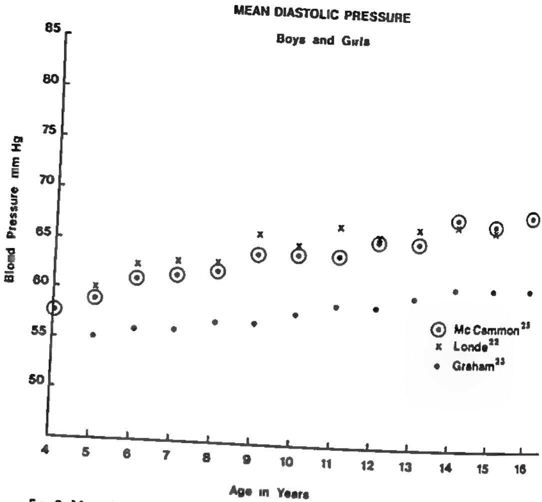

Fig 2 Mean diastolic blood pressures from three separate studies (boys and girls)

Table I Percentile values of blood pressure*

Age (yr)	90%	95%
4 7	115/74	120/78
8 10	122/76	127/80
11 15	133/80	137/82

Summarized from Londe's data

it certainly should be used in newborn nurseries well baby clinics and group pediatric practices

Normal range of blood pressure There have been few comprehensive studies for establishment of normal blood pressure values in children The study of Graham and associates is perhaps the most impressive from two view points (1) a large number of patients (3 580) and blood pressures (25,000) were used and (2) even more important, observer variability was at a minimum because one person measured all the blood pressures Two other recent studies by Londe and McCammon have helped establish further the normal blood pressure range in children Fig 1 shows the mean systolic pressure of these three studies Fig 2 depicts the mean diastolic pressures No attempt has been made to determine if there are any statistically significant differences between the three groups The children studied by Graham were sitting those by Londe and McCammon were supine Cuffs of appropriate size were used and there appears to be little difference between boys and girls levels of blood pressure It is apparent from these studies that blood pressure rises slowly with age systolic pressure more than diastolic Studies such as these also point out the small amount of evidence accumulated regarding normal standards for blood pressure in children from birth to school age and demonstrate the importance of *not* considering 140/90 mm Hg as the level above which children are designated as being hypertensive

Although there is now general agreement as to what is normal blood pressure in childhood there is uncertainty as to what constitutes an adequate definition of hypertension As suggested by Master and associates in their study of adults patients whose blood pressures were occasionally

hypertension has long been recognized In a comprehensive study relating adiposity and blood pressure by Kannel and associates[1] they reported that there was a higher prevalence of hypertension in the obese patient but that obesity was not necessarily the chief determinant factor in those patients who were hypertensive They also showed that while existing hypertension was related to relative weight obese patients who were normotensive initially subsequently developed hypertensive cardiovascular disease at an increased rate In Londe's[1] report of hypertension in apparently normal children he found the prevalence of obesity to be significantly higher in the hypertensive children than in a control group Boyle showed no correlation between obesity and hypertension in blacks while there was a correlation in whites It is apparent that obesity can be one of the multiple factors relating to essential hypertension

Salt. Another factor implicated as a causative factor in essential hypertension has been dietary salt intake Dahl and associates have published several studies suggesting that the level of dietary salt intake may play a role in the development of essential hypertension Dahl and Love[1] postulated that excessive salt intake in infants may predispose them to essential hypertension as adults and thus has suggested that salt additives to processed baby foods be discontinued Guthrie suggested that infant foods be manufactured which are markedly lower in salt content than those currently available The study by Prior and associates of two Polynesian populations with different salt intakes supported Dahl's hypothesis that increased salt intake and higher blood pressures are related A majority of people however ingest a large amount of salt without developing hypertension and many hypertensive patients remain hypertensive despite severe salt restriction In a recent article by the Committee on Nutrition American Academy of Pediatrics reviewing current thinking about salt intake and blood pressure in children the following statements were made (1) The Committee recommends actions that reduce or avoid increasing the present level of salt intake by children in the population at large (2) Children with a family history of hypertension may benefit from a low salt diet although the evidence is incomplete (3) There is a reasonable possibility that a low salt intake begun early in life may protect to some extent persons at risk from developing hypertension Thus there is suggestive but not conclusive evidence that salt intake plays a role in the development of essential hypertension It is more than likely one of the main contributing factors in those children who may be genetically predisposed to hypertension

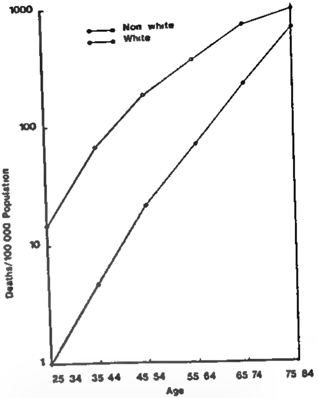

Fig 3 Age-specific death rates for hypertension with and without heart disease by race both sexes combined Death rates are plotted on a logarithmic scale (From Rose J Chron Dis. 16 373 1963)

Race It has been known for several years that the incidence of hypertensive disease is markedly higher in adult blacks than in adult whites but there is very little information dealing with this possible racial difference of blood pressure levels in children Fig 3 graphically demonstrates the death rates from hypertension by race showing a strikingly higher death rate for nonwhites Rose recorded blood pressures of 277 black children in the tenth grade and compared his results with published data on white children He found that the mean pressures of the black children were low by comparison with those of the white children In a more comprehensive and meaningful study Comstock[8] showed little difference in blood pressures between blacks and

Table II Essential hypertension

Ref No	Age (yr)	Definition of hypertension	Per cent with essential hypertension
41	4-18	Ninetieth percentile for age and sex	93
49	< 40	–	25
50	0-14	Diastolic > 120 mm Hg	[illegible]
51	12-40	Diastolic > 100 on two or more occasions	43
52	12-40	> 140/90 mm Hg	86
53	7-32	Elevated diastolic pressure for age	36
54	<35	>140/90 mm Hg	37

hypertension to be 43 per cent Breckenridge and associates investigated 229 hypertensive patients under 40 years of age and found the incidence of essential hypertension to be 68 per cent Takeuchi [4] in a study in Japan investigated patients with hypertension who were less than 35 years of age and found an incidence of essential hypertension of 37 per cent It is difficult to draw definitive conclusions from these studies because of the different ages and levels of blood pressure but it looks as if the incidence of essential hypertension in children is more prevalent than was thought several years ago

Perhaps the most impressive study relating to essential hypertension in children was done by Londe and associates [41] They investigated 74 children 4 to 18 years of age whose blood pressures were consistently above the ninety fifth percentile for age and sex The first 33 children were investigated as outpatients and the next 41 children were thoroughly evaluated as inpatients There was no significant difference in the findings in the two groups and the over all incidence of essential hypertension was 93 per cent The prevalence of obesity and of parental hypertension was higher in the hypertensive children than in the normotensive children The findings of these studies are depicted in Table II

Epidemiology of essential hypertension

It is generally well accepted that most hypertensive adults have essential hypertension [55] Although most of the investigative work regarding the epidemiology of essential hypertension has related to adults evidence continues to mount to suggest that essential hypertension may have its onset in early life [56] Many factors have been implicated as playing a role in the epidemiology of essential hypertension including genetic and hereditary influences atherosclerosis, body stature, dietary salt intake racial predisposition and environmental and psychosocial factors

Genetic and hereditary factors Smirk and Hall[5] described a form of hypertension in rats in which the hereditary factor is clear cut Platt [6] felt that hereditary factors are the primary cause of essential hypertension—that it relates to a single autosomal gene On the other hand Pickering[7] felt that blood pressure is influenced by a constellation of genetic factors which are modified by environmental influences Further investigation needs to be done in an attempt to determine if a child is born with a certain genetic makeup [8] relating to essential hypertension

Familial factors Evidence continues to accumulate showing a strong familial influence on the development of essential hypertension [9-13] Zinner and associates [9] have published data that demonstrate a familial influence on blood pressure in childhood Their data suggest that familial tendencies for hypertension are established early in life Lieberman[6] makes a crucial point of reminding pediatricians to conduct a thorough family history looking for the presence of hypertension stroke, or coronary artery disease in younger family members If any of these factors are present these children are at greater risk for developing hypertension

Atherosclerosis There have been numerous articles recently concerning the complex interwoven mesh between atherosclerosis and hypertension particularly as it relates to children Kannel and Dawber stated that atherosclerosis and hypertension have their origins in infancy and childhood The exact determining factors of blood lipids and their relationship to hypertension and atherosclerosis are uncertain There is mounting evidence however that excessive dietary fat and carbohydrate intake may play a significant role in the development of atherosclerosis and hypertension Blumenthal and Jesse [8] put the issue of atherosclerosis in its proper perspective, stating that it appears to be a pediatric problem, and that greater emphasis needs to be placed on early detection and perhaps treatment of the child who is at risk for atherosclerosis and hypertension

Obesity The relationship between obesity and

ciates, Perera followed 30 young adults with essential hypertension for an average of 20 years. Eight patients (37 per cent) died after a mean survival period of 21 years after diagnosis. Of the remaining 22 patients, 15 had hypertensive complications and this figure combined with the eight deaths would suggest that elevated blood pressures at an early age suggest a poor prognosis. Diehl and Hesdorffer[9] reported on the follow up of men who were found to be hypertensive in college and found that those with elevated systolic blood pressures initially were more likely to have elevated systolic blood pressures than those who were normal initially. Julius and associates followed 208 male college students retrospectively after an average 20 year interval and found that (1) The over all incidence of hypertension initially was the same (13 per cent) as it was after a 20 year follow up (14 per cent). (2) There was poor correlation between the initial and final readings for an individual subject. (3) There appeared to be a relationship between obesity and hypertension. In perhaps the most meaningful study pertaining to children Heyden and associates studied a group of 435 adolescents looking for evidence of elevated blood pressures. Fifty adolescents (11 per cent) were found to have hypertension, systolic levels greater than 140 mm. Hg and/or diastolic levels greater than 90 mm. Hg. Thirty people were re-evaluated 7 years later: 12 (40 per cent) had lower blood pressures, 7 (23 per cent) had pressures which were unchanged, and the remaining 11 (37 per cent) had either sustained (greater than 160 mm. Hg and/or 95 mm. Hg) hypertension or vascular complications (including death in two patients). This study would suggest that hypertension discovered at a young age can be indicative of future hypertensive disease. The evidence is conflicting but it would appear that although a significant percentage of young people with a single elevated blood pressure reading will not develop hypertension as adults, an unusually high percentage of those with elevated blood pressures will develop frank hypertension and the complications associated with this entity.

Table IV Basic laboratory studies for diagnosis of persistent hypertension*

Study	*Cause of hypertension suggested by abnormal tests*
Urinalysis and urine culture	May be helpful in chronic bilateral or unilateral renal parenchymal disease
Hemoglobin, hematocrit, white blood cell count, and differential count, CO, Cl, Na, K, BUN, creatinine, Ca, P	May be helpful in chronic renal disease, hypercalcemia, aldosteronism (primary or secondary), adrenogenital syndrome
Plasma renin	May help differentiate between high and low renin hypertension
2 hr. postprandial blood sugar	May be increased in Cushing's disease, pheochromocytoma
Immunoelectrophoretic analysis	β C globulin may be decreased in acute poststreptococcal glomerulonephritis, progressive or persistent hypocomplementemic nephritis, nephritis of lupus erythematosus
Chest x-ray and ECG	
24 hr. urine collection for norepinephrine, epinephrine, metanephrines, vanillylmandelic acid (VMA), dopamine, homovanillic acid (HVA)	Increased in neuroblastoma and pheochromocytoma; abnormal VMA/HVA ratio in familial dysautonomia
24 hr. urine collection for 17-hydroxysteroids and 17-ketosteroids	Cushing's disease, adrenogenital syndrome
Aldosterone secretion rate or aldosterone excretion	Increased in aldosteronism
Fast sequence intravenous pyelogram	May be abnormal in unilateral or bilateral renal parenchymal disease, renovascular hypertension, neuroblastoma, Wilm's tumor
Abdominal aortogram	May be helpful in unilateral renal parenchymal disease, pheochromocytoma; helpful in abdominal coarctation and renal artery lesions
Renal vein renins	May be helpful in unilateral renal parenchymal disease and renal artery lesions

*Modified from Loggie: Pediatr. Clin. North Am. 18: 1273, 1971.

Etiology and evaluation of secondary hypertension

The question still persists: Does a child with mildly elevated blood pressures require a thorough and expensive hospital evaluation? In Loggie's study, 33 hypertensive children were evaluated as out patients and 41 children were hospitalized and evaluated. No apparent cause of hypertension was noted in 69 children (93 per cent). This author along with others (personal communication) has been impressed with the lack of findings in mildly hypertensive children who have been subjected to extensive investigation. These observations raise doubts about the

Table III Causes of secondary hypertension in children

Cardiovascular
- Coarctation of the aorta[1]
- Patent ductus arteriosus
- Aortitis
- Bacterial endocarditis

Renal
- Pyelonephritis
- Hydronephrosis[1]
- Tumors[1]
- Glomerulonephritis
- Renal artery abnormalities
- Renal vein thrombosis
- Trauma
- Post renal transplant
- Hypoplastic kidney
- Ureteral obstruction
- Ectopic kidney
- Interstitial nephritis

Endocrine
- Cushing s syndrome
- Pheochromocytoma[1]
- Neuroblastoma
- Primary aldosteronism
- Adrenogenital syndrome
- Hyperthyroidism
- Hyperparathyroidism
- Corticosteroid therapy
- Renin related hypertension

Miscellaneous
- Lead poisoning
- Mercury poisoning
- Poliomyelitis
- Radiation therapy
- Encephalitis
- Brain tumor
- Stevens-Johnson syndrome
- Guillain Barré syndrome
- Post genitourinary surgery
- Burns
- Reserpine overdose
- Marfan s syndrome
- Licorice ingestion
- Methyl dopa infusion
- Hypercalcemia
- Ocular phenylephrine

whites up to the age of 15 years but thereafter at all ages blacks had higher mean blood pressure than whites These studies would suggest that black and white children have comparable blood pressures but at some time in young adulthood the difference becomes significant Further investigations need to be done to substantiate this finding Dube and associates measured blood pressures in 1,668 black children aged 4 to 17 years Maximum systolic and diastolic pressures were higher in their group of patients wh compared to previously reported results of whi children of similar ages It is apparent that the are many unanswered questions relating to rac differences and longitudinal prospective studi need to be done looking at (1) Is there a diffe ence in blood pressures of white and black ch dren when measured under comparable con tions? (2) Is there a form of hypertension to whi blacks are particularly predisposed? (3) If blo pressures of black and white children are comp rable what events occur which make adult blac particularly susceptible to hypertension?

Numerous other factors have been discussed possibly playing a role in the development essential hypertension These include smokin exercise environmental surroundings and ps chosocial stress These have been well discussed recent papers by Henry and Cassel and Stamler and associates It is difficult to dra any definitive conclusions about the epidemi ogy of essential hypertension in adults but it h become increasingly apparent that many of t factors which relate to essential hypertension adults have their onset in childhood

Natural history The natural history of hype tension in children is poorly documented There a need for longitudinal study in which childr with elevated blood pressures are followed ar two questions are answered (1) Do a significa percentage of these children develop essenti hypertension as adults? (2) Does treatment these children have a significant effect in reduci the morbidity that is associated with untreat hypertension in adults? There has been a gre deal of controversy surrounding the prognosis elevated pressures in children and young adult This stems mainly from the lack of da concerning this issue There are those who ha felt that elevated blood pressures in a child do n necessarily predict a future potential for hype tension Other studies have show somewhat conflicting evidence regarding th prognosis of elevated blood pressures in childre and young adults Most of the studies invol young adults however rather than children

Stewart reported a series of 40 men wit essential hypertension with an average age of 3 years who were followed for an average of 6 to years Twelve (30 per cent) men s pressures fell t a normal range without treatment suggestin that a significant number of men with eleva blood pressures will progress to normotensi

Table V Oral therapy of essential hypertension

Drug	Dose	Side effects	Comments
Reserpine	0.25-0.5 mg./day	Nasal stuffiness depression	May take several days for hypotensive effect
Hydralazine	10-100 mg./day	Headache palpitation	Rapid onset and short duration Should be given q i d
Methyldopa	500 mg ? Gm /day	Somnolence postural hypotension bradycardia	Advantage—can be given once a day
Guanethidine	10-60 mg./day	Postural hypotension exercise hypotension	
Chlorothiazide	250 mg 1 Gm /day	Hypokalemia hyperuricemia	Effective can be given once or twice a day

are obese and there is little encouragement or support from the family for the child to lose weight. (?) The children are salt restricted to 2 or ? Gm of NaCl per day depending on their age (?) The use of antihypertensive agents is begun in a stepwise fashion beginning with the mildest medication (usually the thiazide diuretics) Table V lists some of the drugs which are used at this hospital for control of hypertension Several other articles cover this aspect in greater depth. As mentioned above we begin in a stepwise fashion often waiting several weeks and evaluating several blood pressure readings before assessing the effect of that medication Our ultimate goal is a normal blood pressure with a *single* medication with no or minimal side effects It has been our experience that we have much better patient compliance with the therapeutic regime if we can control the patient s blood pressure with a single medication

Conclusions

1 The measurement of arterial blood pressure should be an integral part of every child s physical examination Proper use of currently available equipment results in accurate measurements.

2 If a child is discovered to have an elevated blood pressure repeated measurements with the proper size cuff are necessary to definitely establish the presence of hypertension

3 Children with a familial history of essential hypertension are at increased risk for developing hypertension Thus a child with well documented hypertension should have a thorough inquiry concerning hypertension in the family If the child is obese proper dietary therapy should be undertaken in order to reach a more desirable weight

4 If a child has mildly elevated blood pressures and a family history of hypertension and/or is obese there is a strong likelihood that this is essential hypertension An investigative workup is likely to be noninformative in this type of child

5 A child with persistent elevated blood pressures above the ninety fifth percentile who has no family history of hypertension and is not obese deserves a thorough search for an underlying etiology

6 The value of treating a child with mild labile hypertension has not been definitely shown It would seem advisable on the basis of current evidence to advise this type of child about a low salt diet and encourage proper weight control Repeated blood pressure measurements are essential for if the pressure becomes fixed antihypertensive medication is indicated

7 On the basis of data from adults with fixed hypertension it seems reasonable to advise that children with persistent elevated hypertension greater than the ninety fifth percentile should be treated with antihypertensive medications Current evidence suggests that this type of therapy will decrease the morbidity and mortality rates associated with long standing hypertension

REFERENCES

1 McCrory W W and Nash F W Hypertension in children A review Am J Med Sci. 223 6/1 1952
2 Oliver W J Talnor N S and Stern A M Hypertension in infancy and childhood J Mich State Med Soc 59 82, 1960
3 Slater R J Geiger D W Azzopardi P and Webb B W Hypertension in children Can Med Assoc J 81 1 1959
4 Lieberman E and Holliday M A Acute and chronic hypertension in infants and children Diagnosis and management Pediatr Portfolio 2 ? 13 2
5 Loggie J M Systemic hypertension in children and adolescents Pediatr Clin North Am 18 12 3 1971

necessity of inpatient evaluation of mildly hypertensive children. If a child is found to be mildly hypertensive on repeated examinations with the proper size cuff, special notice should be taken of obesity in the child and/or his family and intensive questioning regarding parental hypertension must be done. A thorough physical examination must be performed, including measuring the blood pressures in the lower extremities and listening for abdominal bruits. A urinalysis should be done on a concentrated specimen, a creatinine clearance measured, and an ECG and chest film should be obtained. If obesity and/or parenteral hypertension are present and if the physical examination and laboratory studies yield normal results, it may be of the best interests of the patient to do no further testing.

The physician will occasionally be faced with a child with a persistent significantly elevated pressure. There is a general agreement that this child should be hospitalized and an extensive evaluation should be undertaken. There is evidence which suggests that the higher the elevation of blood pressure the more likely an etiology can be found. Table III lists many of the multiple causes of secondary hypertension in children. Table IV lists the basic laboratory studies for the diagnosis of persistent hypertension. The physician caring for a hypertensive child should keep in mind that a complete workup such as outlined in Table III can be a time consuming and expensive experience. If a diagnostic clue is discovered in the history, the physical examination, or the initial outpatient laboratory evaluation, the inpatient evaluation can be modified considerably. For more extensive information on the etiologic evaluation of hypertension the articles by Loggie and Gifford are helpful.

Treatment

Any child with elevated blood pressures due to secondary causes should have the appropriate measures taken if possible to cure the condition causing the hypertension. The real dilemma occurs when a physician is faced with a child with essential hypertension. Should this child be treated? Does treatment alter the morbidity that is associated with long standing hypertensive disease? Unfortunately, these questions cannot be definitely answered at this time. There is an ongoing disagreement among many physicians concerning the efficacy of treating adults with essential hypertension. Chasis stated, "The ultimate value of antihypertensive drug treatment has not been established for the general hypertensive population." Physicians must also consider the psychologic impact of telling a child or adolescent he has a chronic disease and may have to take medication for the rest of his life. It is well known that there are many undesirable side effects to antihypertensive medications. One of the leading proponents of the value of treating essential hypertension has been Freis. He stated in a recent editorial "... if the blood pressure is controlled this progression of cardiovascular disease is considerably reduced or prevented."

In looking at both sides of the controversy, perhaps a point should be made about the different prognostic outlooks for adults with labile hypertension and those with "fixed" hypertension. Mathisen and associates have shown that the death rate for adult men with "fixed" hypertension was five times that of adult men with labile hypertension. In attempting to relate this to children the following recommendations can be made: (1) At this time no definitive statement can be made regarding the value of treating mild labile hypertension in children. Considering the psychologic impacts of long term antihypertensive medication and the possible undesirable side effects of such medications, perhaps weight control and dietary salt reduction, where applicable, are the appropriate modes of therapy for these children. These children need careful prolonged follow up and a randomized longitudinal prospective study is needed to determine the value of antihypertensive therapy in this group. (2) It appears to this author that there is convincing evidence showing the beneficial effect of antihypertensive therapy in adults with "fixed" hypertension. It seems reasonable to apply this line of reasoning to the treatment of constant "fixed" hypertension in children. Thus if a child has persistent elevated blood pressures above the ninety fifth percentile and an investigative workup is negative, it seems advisable to initiate antihypertensive therapy.

The following guidelines have been used at The Children's Hospital in Denver for antihypertensive therapy: (1) If the patient is obese an ideal weight is selected and the patient and their family consult with our dietitians. We have met with mixed success in this aspect for often the parents

patient with emphasis on detecting curable causes, Milbank Mem Fund Q 47 1 0 1969

Kass, E. H and Zinner S H How early can the tendency toward hypertension be detected? Milbank Mem. Fund Q 47 143 1969

Smirk, F H and Hall W H Inherited hypertension in rats, Nature 182 ? 1958.

Platt, R Heredity in hypertension Q J Med 16 111 1947

Pickering G High blood pressure New York 1968 Grune & Stratton, Inc.

Reynolds, J L Essential hypertension A childhood disease? J La. State Med Soc 125 53 1973

Thomas, C B Familial pattern in hypertension and coronary heart disease Circulation 20 ?5 1959

Chazan J A and *Winkelstein W Household aggregation of hypertension* Report of a preliminary study J Chron Dis 17 9 1964

Gearing, F R, *Clark, E G Perera G A and* Schweitzer M [illegible] Hypertension among relatives of hypertensives Progress report of a family study Am J Pub Health [illegible] 2058 1962

Allan, W Heredity in hypertension Arch Intern Med 52 ?54 1933

Johnson, B C *Epstein F H and Kjelsberg M O* Distribution and familial studies of blood pressure and serum cholesterol levels in a total community—Tecumseh, Michigan J *Chron Dis* 18 147 1965

Zinner S H Levy P S and Kass E H Familial aggregation of blood pressure in childhood N Engl J Med. 284 401 19 1

Lieberman E Essential hypertension in children and youth A pediatric perspective J Pediatr 85 1 19 4

McGill H C *Mitchell S C and Lauer R M The* pediatric challenge of atherosclerosis Children Are Different 8 2, 19 4

Moon, H D Coronary *arteries in fetuses infants* and juveniles Circulation 16 763 195?

Drash, A and Hengstenberg F The identification of risk factors in normal *children in the development of* arteriosclerosis Ann Clin Lab Sci 2 348 1972

Glueck C J and Tsang R C Pediatric familial type II hyperlipoproteinemia Effects of diet *on plasma choles*terol in the first year of life Am J Clin Nutr 25 ?24 972

Strong, J P and McGill H C *The pediatric aspects of* atherosclerosis, J Atheroscler Res 9 ?51 1969

Kannel, W B Castelli W P Gordon T and McNamara, P M Serum cholesterol lipoproteins and the risk of coronary heart disease Ann Intern Med 74 1 19 1

Hollander W Hypertension antihypertensive drugs and atherosclerosis, Circulation 48 1112 19 3

Blumenthal S Prevention of atherosclerosis Am J Cardiol. 31 591 19 3

Schubert W K Fat nutrition and diet in childhood Am. J Cardiol. 31 581 19?3

Kannel, W B and Dawber T R Atherosclerosis as a pediatric problem J Pediatr 80 544 19 2

Blumenthal S and Jesse M J *Prevention of athero*sclerosis A pediatric problem Hosp Pract 8 81 19 3

Pickering G W High blood pressure London 1955 Churchill Livingstone

Hahn, L The relationship of blood pressure to weight height and body surface area in school boys ages 11 to 15 years, Arch. Dis. Child 27 43 19 2

Kannel, W B Brand N Skinner J J Dawber T R and McNamara P M The relation of adiposity to blood pressure and development of hypertension Ann Intern Med. 67 48 196

82 Boyle E Jr Biological patterns in hypertension by race sex body weight and skin color J A M A 213 163? 1970

83 Dahl L K and Love R A Evidence for relationship between sodium (chloride) intake and human essential hypertension Arch Intern Med 94 525 1954

84 Dahl L K and Love R A Etiological role of sodium chloride intake in essential hypertension in humans, J A M A 164 397 1957

85 Dahl L K Salt and hypertension Am J Clin Nutr 25 231 19?2

86 Dahl L K Salt in processed baby foods Am J Clin Nutr 21 ?8 1968

87 Kundsen K D and Dahl L K Essential hypertension Inborn error of sodium metabolism? Postgrad Med J 42 148 1966

88 Dahl L K Heine M Leitl G and Tassinari L Hypertension and death from consumption of processed baby *foods* by *rats Proc Soc Exp* Biol. Med 133 405 19 0

89 Guthrie H A Infant feeding practices—a predisposing *factor in hypertension?* Am J Clin Nutr 21 863 1968

90 Prior I A M Evans J G Harvey H P B Davidson F and Lindsay M *Sodium intake and blood pressure* in two Polynesian populations N Engl J Med 279 515 1968

91 *Committee on Nutrition—American Academy of Pedi*atrics Salt intake and eating patterns of infants and children in relation to blood pressure Pediatrics 53 115 1974

92 Wilber J A Millward D Baldwin A Capron B Silverman D James L M Wolbert T and *McCombs N J Atlanta community high blood pres*sure program methods of community hypertension screening Circ Res 30/31 (Suppl 2) 11 19?2

93 McMahon F G Cole P A *and Ryan J R A study* on hypertension in the inner city AM HEART J [illegible] 3

94 *Langford* H G Watson R L *and Douglas B H* Factors affecting blood pressure in population groups, Trans Assoc Am Physicians 82 135 1968

95 *Rose G A study of blood pressure among Negro school* children J Chron Dis 15 373 1965

96 Comstock, G W An epidemiologic study of blood *pressure levels in a biracial community in the southern* United States Am J Hyg 65 271 1957

97 Dube S K Kapoor S Ratner H and Tunick F Blood pressure studies in black *children (abstract)* Pediatr Res 8 348 19 4

98 Henry J P and Cassel J C Psychosocial factors in essential hypertension Am J *Epidemiol* 90 171 1969

99 Stamler J Stamler R and Pullman T N The epidemiology of hypertension New York 1967 *Grune &* Stratton Inc

100 Stewart I G *Long term observations on high blood* pressure presenting in fit young men Lancet 1 355 19?1

101 *Julius S and Schork M A* Borderline hypertension—a critical review J Chron Dis 23 23 1971

102 Perera G A The course of primary hypertension in the *young, Ann Intern Med. 49 1348 1958*

103 Paul O Risk of mild hypertension *A ten year report* Br Heart J 33 (suppl) 116 1971

104 Diehl H S *and Hesdorffer M D* Changes in blood pressure of young men over a seven year period Arch Intern Med. 52 948 1933

105 Julius S Harburg E *McGinn N F*, Keyes J and Hoobler S W Relation between casual blood pressure

6 Garfunkel J M Hypertension in apparently normal children (editorial) J Pediatr 78 733 1971
7 Clayton G W and Hughes J G Variations in blood pressure in hospitalized children J Pediatr 40 462 1952
8 Frohlich E D Emmott C Hammarsten J F Linehan W M Pollack D and Horsley A W Evaluation of the initial care of hypertensive patients J A M A 218 1036 1971
9 Davis J O The symposium on hypertension (editorial) Hosp Pract Jan 1974
10 Kannel W B Wolf P A Verten J and McNamara P M Epidemiologic assessment of the role of blood pressure in stroke—The Framingham Study J A M A 214 301 1970
11 McKee P A Castelli W P McNamara P M and Kannel W B The natural history of congestive heart failure—The Framingham Study N Engl J Med 285 1442 1971
12 Kannel W B Castelli W P McNamara P M McKee P A and Feinleib M Role of blood pressure in the development of congestive heart failure—The Framingham Study N Engl J Med 286 781 1972
13 Cooperative study Effects of treatment on morbidity in hypertension J A M A 202 116 1967
14 Cooperative study Effects of treatment of morbidity in hypertension J A M A 213 1143 1970
15 Day R Blood pressure determination in children—The effect of the width of the cuff J Pediatr 14 148 1939
16 Woodbury R A Robinow M and Hamilton W F Blood pressure studies on infants Am J Physiol 122 472 1938
17 Long M Dunlop J R and Holland W W Blood pressure recording in children Arch Dis Child 46 636 1971
18 Recommendations for human blood pressure measurements by sphygmomanometers A statement of the committee of the American Heart Association to review standardization of blood pressure reading J A M A 147 632 1957
19 Steinfeld L Alexander H and Cohen M L Updating sphygmomanometry Am J Cardiol 33 107 1974
20 Korotkov M S Mitt Klin Med Kod (St Petersburg) 11 365 1905
21 Moss A J and Adams F H Problems of blood pressure in childhood Springfield Ill 1962 Charles C Thomas Publisher
22 Londe S Blood pressure in children as determined under office conditions Clin Pediatr 5 71 1966
23 Graham A W Hines E A and Gage R P Blood pressures in children between the ages of five and sixteen years Am J Dis Child 69 203 1945
24 Londe S Blood pressure standards for normal children as determined under office conditions Clin Pediatr 7 400 1968
25 McCammon R W Human growth and development Springfield Ill 1970 Charles C Thomas Publisher
26 Hamilton W F Woodbury R A and Harper H T Physiologic relations between intrathoracic intraspinal and arterial pressure J A M A 107 853 1936
27 Recommendations for human blood pressure determination by sphygmomanometers Committee of the American Heart Association Circulation 36 980 1967
28 Goldring D and Wohltmann H Flush methods for blood pressure determinations in newborn infants J Pediatr 40 285 1952
29 Moss A H Liebline W Austin W O and Adams F H An evaluation of the flush method of determining blood pressure in infants Pediatrics 20 53 1957
30 Moss A J Liebline W and Adams F H The flush method for determining blood pressure in infants I Normal values during the first year of life Pediatrics 21 950 1958
31 Uming N L and Reynolds J W Reliability of flush blood pressure measurements in the sick newborn infant J Pediatr 84 594 1974
32 McLaughlin G W Kirby R R Kemmerer W T and deLemos R A Indirect measurement of blood pressure in infants utilizing Doppler ultrasound J Pediatr 79 300 1971
33 Kirkland R T and Kirkland J L Systolic blood pressure measurement in the newborn infant with the transcutaneous Doppler method J Pediatr 80 5 1972
34 Elseed A M Shinebourne E A and Joseph M C Assessment of techniques for measurements of blood pressure in infants and children Arch Dis Child 48 93 1973
35 Dweck H S Reynolds D W and Cassady G Indirect blood pressure measurement in newborns Am J Dis Child 127 492 1974
36 Kirby R R Kemmerer W T and Morgan J C Transcutaneous Doppler measurements of blood pressure Anesth Analg 31 86 1969
37 Blood pressure levels of children 6 11 years Relation to age sex race and socioeconomic status Vital Health Stat 11 135 1973
38 Kilcoyne M M Richter R W and Alsop P A Adolescent hypertension Circulation 50 758 1974
39 Allen Williams G M Pulse rate and blood pressure in infancy and early childhood Arch Dis Child 20 1 1945
40 Master A M Dublin L I and Marks H H The normal blood pressure range and its clinical implication J A M A 144 1464 1950
41 Londe S Bourgoinie J J Robson A M and Goldring D Hypertension in apparently normal children J Pediatr 78 569 1970
42 Londe S and Goldring D Hypertension in children (editorial) AM HEART J 84 1 1972
43 North A F Letter to Editor J Pediatr 79 510 1971
44 Masland R P Heald F P Goodale W T and Gallagher J R Hypertension and vascular disease in adolescence N Engl J Med 255 894 1956
45 Buck C W The persistence of elevated blood pressure first observed at age five J Chron Dis 26 101 1973
46 Loggie J M H Hypertension in children and adolescents J Pediatr 74 331 1969
47 Haggerty R J Maroney M W and Nadas A S Essential hypertension in infancy and childhood Am J Dis Child 92 535 1956
48 Rosenheim M L Hodson C J Edwards D and Williams D I Hypertension in childhood Proc R Soc Med 54 1093 1961
49 Platt R Severe hypertension in young persons Q J Med 17 83 1948
50 Still J L and Cottom D Severe hypertension in childhood Arch Dis Child 43 34 1967
51 Ooi B S Chen B T M Toh C C S and Khoo O T Causes of hypertension in the young Br Med J 3 1970
52 Breckenridge A Preger L Dollery C T and Laws J W Hypertension in the young Q J Med 36 549 1967
53 Singh S P and Page L B Hypertension in early life Am J Med Sci 253 255 1967
54 Takeuchi J Etiology of juvenile hypertension Jap Circ J 30 178 1965
55 Gifford R W Jr Evaluation of the hypertensive

1 Page, L. B., and Crawford J D Childhood hypertension Etiology investigation and treatment, Clin Pediatr 5 39 1966

1 Bongiovanni, A M and Root A W The adrenogenital syndrome N Engl J Med 268 1 83 134? 1963

.. Vazquez A M Nephrocalcinosis and hypertension in juvenile primary hyperparathyroidism Am J Dis Child 125 104 19 ?

3 Bennett S P Levine L S Siegal E I Lewy J E Susin M Peterson R E and New M I Juvenile hypertension caused by overproduction of renin within a renal segment, J Pediatr 84 689 1974

4 Conn J W Cohen E L McDonald W J Blough W M Jr Lucas C P Mayor C H Eveland W C Boodstein J J and Lapides J The syndrome of hypertension hyperreninemia and secondary aldosteronism associated with renal juxtaglomerular cell tumor (primary reninism) J Urol 109 349 19 3

5 Grunkin, A B Linshaw M Cote M L and Fleisher D S Low renin essential hypertension—another form of childhood hypertension J Pediatr 78 6 1971

6 Riley C M Familial dysautonomia Adv Pediatr 9 15? 1957

? Ostfeld A M Sustained hypertension after poliomyelitis, Arch Intern Med 107 551 1961

8 Colquhoun J Hypoplasia of the abdominal aorta following therapeutic irradiation in infancy Radiology 86 454 1 66

9 Bereus, S C Linde L M and Goodwin W E Transitory hypertension following urologic surgery in children Pediatrics 38 194 1966

30 Harrison T Adrenaline and noradrenaline excretion following burns, J Trauma 7 137 1967

31 Lowrey G H Hypertension in children with burns J Trauma 7 140 1967

16? Loggie J M H Saito H Kahn I Fenner A., and Gaffney T E Accidental reserpine poisoning Clinical and metabolic effects, Clin Pharmacol Ther 8 69? 1967

163 Loughride L Renal abnormalities in the Marfan syndrome Q J Med 28 531 1959

164 Koster M and David G K Reversible severe hypertension due to licorice ingestion N Engl J Med 278 1381 1968

165 McNicholl B and Kilroy M K Transient hypertensive encephalopathy Possible relation to licorice J Pediatr 74 963 1969

166 Feldman W Hillman D Baliah T., and Drummond K N Hypertension and seizures following methyldopa infusion, Pediatrics 39 80 1967

167 Nelson W E Textbook of pediatrics Philadelphia 1969 W B Saunders Company

168 Borromeo McGrail V Bordiuk J M and Keitel H Systemic hypertension following ocular administration of 10% phenylephrine in the neonate Pediatrics 51 1032, 1973

169 Page I H Arterial hypertension in retrospect Circ Res 34 133 1974

170 Page I H editor The treatment of essential and malignant hypertension Mod Med March ?0 ?4 197?

1 1 Freis E D The treatment of hypertension Why when and how in Laragh J editor Hypertension manual New York 1974 Dun Donnelley

172 Chasis H Appraisal of antihypertensive drug therapy Circulation 50 4 19 4

173 Freis E D Rebuttal Appraisal of antihypertensive drug therapy Circulation 50 9 1974

174 Mathisen H S Jensen D Loken E., and Loken H The prognosis in essential hypertension AM HEART J 57 3 1 1959

readings in youth and at age 40 J Chron Dis 17 397 1964
106 Heyden S Bartel A G Hames C G and McDonough J R Elevated blood pressure levels in adolescents Evans County Ga J A M A 209 1683 1969
107 Nadas A S Pediatric cardiology Philadelphia 1972 W B Saunders Company
108 Fisher E R and Corcoran A C Congenital coarctation of the abdominal aorta with resultant renal hypertension Arch Intern Med 89 943 1952
109 Loggie J M Gaffney T E Kaplan S and Hanenson I B Hypertension and mitral incompetence associated with multiple systemic and pulmonary artery stenoses in a Caucasian child J Pediatr 72 101 1968
110 Danaraj T J and Ong W H Primary arteritis of abdominal aorta in children causing bilateral stenosis of renal arteries and hypertension Circulation 20 856 1959
111 Issaacson C An idiopathic aortitis in young Africans J Pathol Bacteriol 81 69 1961
112 Gasul B J Glasser J M and Grossman A Extreme hypertension in a child cured by nephrectomy Report of a case and review of the literature J A M A 139 305 1949
113 Kennedy R L J Barker N W and Walters W Malignant hypertension in a child Cure following nephrectomy Am J Dis Child 61 128 1941
114 Kennedy R L J Barker N W Walters W Malignant hypertension Cure following nephrectomy Am J Dis Child 69 160 1945
115 Welch H C Harris L E and DeWeerd J H Nephrectomy in juvenile hypertension associated with renal disease Pediatrics 21 941 1958
116 Silver H K Wilms s tumor (embryoma of the kidney) J Pediatr 31 643 1947
117 Bradley J E and Drake M E The effect of preoperative roentgen ray therapy on arterial hypertension in embryoma (kidney) J Pediatr 35 710 1949
118 Hughes J G Rosenblum H and Horn L G Hypertension in embryoma (Wilm s tumor) Pediatrics 3 201 1949
119 Jagasia K H Thurman W G Pickette I and Grabstadt H Bilateral Wilm s tumor in children J Pediatr 65 371 1964
120 Ganguly A Gribble J Tune B Kempson R L and Luetscher J A Renin secreting Wilm s tumor with severe hypertension Ann Intern Med 79 835 1973
121 Edelmann C M Jr and Barnett H L Pediatric nephrology *in* Strauss M D and Welt L G editors Diseases of the kidney Boston 1971 Little Brown & Company
122 Etteldorf J N Smith J D and Johnson C The effect of reserpine and its combination with hydralazine on blood pressure and renal hemodynamics during the hypertensive phase of acute nephritis in children J Pediatr 48 128 1956
123 Tilford D L and Kelsch R C Renal artery stenosis in childhood neurofibromatosis Am J Dis Child 126 655 1973
124 Sinaiko A Najarian J Michael A F and Mirkin B L Renal autotransplantation in the treatment of bilateral renal artery stenosis Relief of hypertension in an 8 year old boy J Pediatr 83 409 1973
125 Smith J P and Saylor M L Renal vascular hypertension in children J Urol 84 17 1960
126 Presto A J III and Middleton R G Cure of hypertension in a child with renal artery stenosis and hydronephrosis in a solitary kidney J Urol 109 9[illegible] 1973
127 Grossman R E and Babbitt D P Renal artery aneurysms Their diagnosis and endocrine implicatio[illegible] A case report in a child J Urol 97 1[illegible] 196[illegible]
128 Cummings K B Lecky J W and Kaufman J Renal artery aneurysms and hypertension J Ur[illegible] 109 144 1973
129 Long L Javid H and Julian O C Arteriovenous fistula of renal vessels Report of a case believed congenital and review of literature Ann Surg 160 [illegible] 1964
130 Angella J J Sommer L S Poole C and Fogel B Neonatal hypertension associated with renal arte[illegible] hypoplasia Pediatrics 41 524 1968
131 Paulbinskas A J and Wylie E W Roentgen dia[illegible]nosis of fibromuscular hyperplasia of the renal artery Radiology 76 634 1961
132 Halpern M and Currarino G Vascular lesio[illegible] causing hypertension in neurofibromatosis N Engl Med 273 248 1965
133 Klecker R L and Roth J [illegible] Visceral neurofibroma[illegible]tosis and hypertension in childhood Pediatrics 53 [illegible] 1974
134 Cook G T Marshall V F and Todd J E Maligna[illegible] renovascular hypertension in a newborn J Ur[illegible] 96 663 1966
135 Arneil G C MacDonald A M Murphy A V a[illegible] Sweet [illegible] M Renal venous thrombosis Clin Nephr[illegible] 1 119 1973
136 Downs R A and Hewett A L Hypertension due subcapsular renal hematoma J Urol [illegible] 1962
137 Najarian J S Simmons R L Tallent M B Kje[illegible]strand C M Buselmeir T J Vernier R L a[illegible] Michael A F Renal transplantation in infants a[illegible] children Ann Surg 174 583 1971
138 Garrett J Polse S L and Morrow J W Ureter[illegible] obstruction and hypertension Am J Med 49 [illegible] 1970
139 Mininberg D T Roze S Yoon H J and Pearl [illegible] Hypertension associated with crossed renal ectopia an infant Pediatrics 48 545 1971
140 Stickler G B Kelalis P P Burke E C and Seg[illegible] W E Primary interstitial nephritis with reflux cause for hypertension Am J Dis Child 122 1[illegible] 1971
141 Bergstein J M Fargman J Fish A J Herdman [illegible] and Good R A Severe hypertension in identical tw[illegible] infants Am J Dis Child 122 348 1971
142 Forsham P H The adrenal cortex *in* Williams R H editor Textbook of endocrinology Philadelphia 1[illegible]6 W B Saunders Company
143 Rubin M I Systemic hypertension Pediatr Cl[illegible] North Am 11 431 1964
144 Farber S and Vawter G F Clinical pathological co[illegible]ference J Pediatr 67 878 1965
145 Cone T E Allen M S and Pearson H S Pheochr[illegible]mocytoma in children Report of 3 familial cases in tw[illegible] unrelated families Pediatrics 19 44 1957
146 Cone T E and Pearson H S Malignant pheochr[illegible]mocytoma Report of a case in a 12 year old gi[illegible] Pediatrics 32 531 1963
147 Stackpole R H Melicow M M and Uson A C Pheochromocytoma in children Report of 9 cases an[illegible] review of first 100 published cases with follow up stud[illegible]ies J Pediatr 63 314 1963
148 Pickett L K and Voorhess M L Neuroblastoma i[illegible] childhood Surg Clin North Am 44 1469 1964
149 New M I and Peterson R E Disorders of aldoste[illegible]rone secretion in childhood Pediatr Clin North Am 13 43 1966

In the adult heart the sinus node is 10 to 20 mm. long. It lies near the junction of the superior vena cava and the right atrium. Shaped like a flattened ellipse, it occupies a position that is less than 1 mm. beneath the epicardial surface. The physiologic implications of this location are obvious, the node being vulnerable to many conditions which affect the epicardial surface, e.g., pericarditis.

Perhaps the most interesting aspect of the anatomy of the sinus node is its blood supply. This has been carefully studied by James. The primary supply is virtually always a single vessel which arises from the proximal few centimeters of the right coronary artery in about 55 per cent of cases and from the proximal few millimeters of the left circumflex artery in about 45 per cent. In its course, this vessel also serves as the blood supply to a major portion of the atrial myocardium and interatrial septum.

In addition to being disproportionately large, this vessel passes directly through the center of the sinus node, giving off small lateral branches within the node. The central relation to the node is so constant that it has been stated by Soderstrom that the node resembles an enormous adventitia of its own artery. James and Nadeau have commented on the possibility that there is a physiologic relation between the pulsation of the nodal artery and sinus node function. Both the central nodal position of the vessel and its proximal origin from the coronary circulation would tend to support this theory. This location would seem to indicate that changes in central aortic pressure would be transmitted quickly to the nodal artery and thereby to the node itself. Indeed, many observations have shown that drugs and procedures which increase the rate of sinus node discharge may decrease the caliber of the artery, whereas those which slow the node may increase the caliber of the artery.

The sinus node is composed of several types of cells. A dense collagen framework which surrounds the central artery is found to contain interlacing bundles of fibers. The latter converge to existing Purkinje fibers in all directions. At the mid portion of the sinus node, the nodal fibers distribute from stellate cells which have a large round nucleus and are known as P cells. These are thought to be the site of actual pacemaking. Under electron microscopic studies they resemble the leading cells which Harary has shown to be the dominant pacemakers in myocardial fiber tissue cultures.

Although no ganglia are found in the sinus node, it contains numerous nerve endings.

The internodal pathways. It has been shown on electrophysiologic studies that the impulse from the sinus node arrives at the A-V node more rapidly than it would if it traversed ordinary myocardium. This suggests that internodal pathways exist, and indeed three such tracts have been described: the anterior, middle, and posterior internodal tracts. Although intra-atrial conduction may occur along any one of the three, it is preferentially along the anterior tract in most normal hearts. The normal or usual course for internodal conduction is, however, not completely known at present.

Electrophysiology

The pacemaker cells in the sinus node have been studied by microelectrode technique. This method has shown that these and other pacemaker cells possess a unique characteristic, viz., spontaneous diastolic depolarization. This occurs in a cyclical or repetitive fashion. When the decreasing transmembrane potential reaches a critical threshold value during phase 4 depolarization, membrane permeability abruptly changes, sodium ions move into the cell, and the cell is depolarized to zero potential in relation to the surrounding extracellular fluid. Pacemaker cells have a slower depolarization and repolarization process than nonpacemaker Purkinje fibers. After repolarization, depolarization again occurs—after self-excitation. The ionic changes that are associated with this process are not yet entirely clear, but it would seem that decreased outward potassium permeability and inward leakage of sodium are responsible for the spontaneous automaticity that is seen.

The automaticity of the sinus node is responsible for the maintenance of a faster rate of recurring self-excitation than other latent pacemaker sites. Changes in this automaticity are mediated primarily by changes in the rate of phase 4 depolarization. There is a profound influence of the autonomic nervous system on the sinus node rate which varies depending upon the demands of the body. As implied in the foregoing anatomic discussion, the sinus node impulse is a result of the discharge of potentials from many pacemaker cells. The potentials of the cells are

The sick sinus syndrome

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The term 'sick sinus syndrome' has been used to describe a group of clinical states in which one or more of the following signs appeared (1) persistent severe and unexpected sinus bradycardia (2) cessation of sinus rhythm for short intervals with other rhythms supervening (3) long periods of sinus arrest without escape rhythm (4) untreated chronic atrial fibrillation with slow ventricular rate (5) no sinus rhythm after cardioversion, (6) sino atrial (SA) exit block The syndrome has been studied clinically and pathologically and is a well delineated entity

Disorders of the sino atrial node resulting in bradycardia and asystole have been reported by many authors[1-7] Most reports emphasized the bradycardic features of sino atrial dysfunction In 1954 however Short[8] noted an association between bradycardia productive of symptoms and paroxysmal supraventricular arrhythmias Lown[9] first used the term 'sick sinus syndrome' to describe certain arrhythmias following DC cardioversion He had noted chaotic atrial activity, changing P wave contour bradycardia interspersed with multiple and recurrent ectopic beats with runs of atrial and nodal tachycardia Ferrer[10] extended the definition to include the following signs (1) persistent severe and unexpected sinus bradycardia (2) cessation of sinus rhythm for short intervals (sinus arrest) or for longer periods with replacement of this rhythm with ectopic atrial or junctional rhythm (3) long periods of sinus arrest without a new pacemaker arising resulting in periods of total cardiac arrest, (4) chronic atrial fibrillation often accompanied by a slow ventricular rate, the latter not produced by drug therapy (5) failure of heart to resume sinus rhythm after electroversion for atrial fibrillation (6) episodes of SA exit block not related to drug therapy

After Ferrer's description many reports followed and various terms were used to describe these phenomena 'inadequate sinus mechanism,'[11] 'sluggish sinus node syndrome'[12] and 'sino atrial syncope'[13] When an element of tachycardia was associated with the bradycardic aspects the condition has been called the 'syndrome of alternating bradycardia and tachycardia'[8] or 'The bradycardia tachycardia syndrome'[14] (BTS)

Anatomy

The sinus node The sinus node was first described by Keith and Flack[15] in 1907 and its electrophysiologic property as pacemaker of the heart by Wybouw[16] and Lewis and associates[17] in 1910

Walmsley[18] proposed that the pacemaker of the heart be referred to as the sinus node rather than sino atrial or sino auricular node This seems more accurate in view of the fact that this structure is near the junction of both the superior vena cava and the sinus intercavorum with both the atrium and the ventricle

In the embryo the sinus node and atrioventricular (A V) node arise similarly Both structures form at the junction of the right and left superior cardinal veins and the sinus venosus the sinus node appearing in the vicinity of the former and the A V the latter Ultimately the sinus venosus forms the medial half of the right atrium and a portion of the interatrial septum The A V node migrating with the sinus venosus assumes an internal position in the adult heart The sinus node does not migrate for any appreciable distance and therefore retains its primitive position

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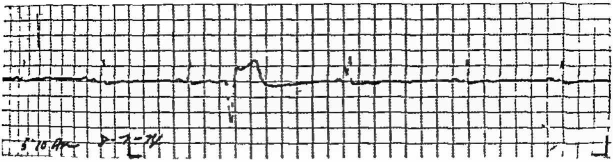

Fig 1 FCG of M C (case 1)

amilial cases have been documented[36 37] and it is robable that there is a small familial incidence of he syndrome

Gambetta Weese Ginsburg and Shapiro eported a patient with the SSS whose family had R prolongation It is interesting however that f 22 familial members studied eight had rolon ed PR and only one the propositus the SS.

athogenesis

As it would appear that ischemic heart disease ccounts for the majority of patients with the SS, it deserves special mention

As previously noted the sinus node is particu rly vulnerable to vascular occlusive disease since it receives its entire blood supply from a single artery It should also be remembered that he same artery supplies most of the atria Occlu sion of this vessel will affect sino atrial electrical activity Indeed sinus node dysfunction occurs in about 5 per cent of acute myocardial infarctions[39] and the sinus node has been found frequently to be infarcted in patients who develop atrial arrhythmias It can be suspected that occlusions of the right coronary artery or circumflex branch of the left coronary artery will be commonly associated with atrial arrhythmias This is in fact, the case and atrial infarction is exceedingly rare with isolated occlusion of the left anterior descending coronary artery

Electrophysiology For the purposes of discus sion of electrophysiology general categories of arrhythmias in the SSS are (1) atrial brady arrhythmias (2) atrial tachy arrhythmias and (3) atrial brady tachy arrhythmias

Atrial brady arrhythmias A reduction in spon taneous activity of the sinus node may result in sinus bradycardia *Also* sino atrial exit block of various degrees may be manifested by sinus bradycardia Complete loss of sinus node function or complete sino atrial exit block will result in atrial standstill or arrest

The phenomenon of sinus bradycardia in the well trained athlete is well known In the patient with symptomatic sinus bradycardis however this arrhythmia may have various physiologic causes These include diminished slope of phase 4 depolarization increase in activation threshold increased or augmented acetylcholine concentra tions reduced catecholamines drugs (such as propranolol) depressed thyroid function and hypothermia Sinus bradycardia is probably the most common single ECG manifestation of the SSS being found in 76 per cent of the reported cases of Radford and Julian , and [illegible] of 56 of the patients cited by Schulman Rubenstein Yur chak and DeSanctis

CASE 1 M C a 72 year old housewife was admitted to the Long Island College Hospital in July 1974 because of syncope She had begun to have angina pectoris about 20 years prior to admission Nitroglycerin was given to her by her private physician Four years prior to admission sudden shortness of breath and severe chest pain necessitated admis sion to another hospital, where she was told that she had had an acute myocardial infarction Digitalis and diuretic therapy was started and she continued the former medication until the present admission

In the 2 years prior to admission the patient began to have syncopal episodes These were infrequent at first but in the 2 months prior to admission two to three episodes per week occurred The syncopal attacks were not associated with chest pain or palpitations, and each lasted 1 to 2 minutes.

On physical examination the vital signs were normal except for a pulse of 56 per minute Examination of the heart revealed a regular rhythm and no murmurs were heard. An atrial gallop (S) was audible at the cardiac apex The remainder of the physical examination was within normal limits. An ECG on admission showed sinus bradycardia and evidence of old anteroseptal myocardial infarction Digitalis blood levels were 0.2 ng. per milliliter Sinus bradycardia persisted and the

slow rising associated with slow conduction and vulnerable to block Moreover conduction within the node itself may be inhibited by the stroma and, in the perinodal tissue, the impulse may also become blocked The latter may occur despite the presence, in the perinodal tissue, of a cell population that seems to act as an amplifier for exiting impulses

Pathology and etiology

There have been few pathologic studies in cases of the sick sinus syndrome (SSS) The conduction system was studied by Cohn and Lewis in a patient with auricular fibrillation and complete heart block These authors found that the upper end of the SA node was destroyed there was fatty infiltration of the SA node, the atria were dilated and focally fibrotic and the A V node was normal Rasmussen reported a case of SA block in which he found extensive fibrosis of the SA node and SA junction Kaplan Langendorf Lev and Pick described the pathologic findings in two patients of the 10 whom they reported In one case, the SA nodal artery arose from the right coronary artery, both of which showed no narrowing On histologic examination, some arterioles in the SA node showed narrowing acute degeneration or necrosis All the approaches to the SA node showed fibrosis and elastosis In addition chronic inflammation of the A V node was found In their second case edema and hemorrhage of the elastic and collagen fibers of the SA node were noted The approaches of the SA node had moderate arteriolosclerosis and focal degeneration of muscle cells This case was one of amyloid heart disease and amyloid deposits were found in the left atrium Careful examination of the conduction system of atrium and ventricle however, failed to show amyloid infiltration Allensworth Rice and Lowe [8] reported amyloid deposits in the myocardium in two patients with persistent atrial standstill Rasmussen felt that diphtheria was the etiologic factor in his case and the two patients reported by Vouvram, Slama and Temkine[4] developed the sick sinus syndrome during an attack of diphtheria

Although pathologic studies are meager many cases of the SSS would appear to occur in patients with coronary artery disease Indeed, in the report of Rubenstein, Schulman Yurchak and DeSanctis' this was the most common [illegible]lished etiology, being found in 20 of 56 pa[illegible] These authors pointed out however, that in 2[illegible] their patients no etiology for the syndrome c[illegible] be found Coronary artery disease as an eti[illegible] factor, will be discussed further under pathoge[illegible]sis

Although cardiomyopathy has occasion[illegible] been reported to be a cause in the product[illegible] the bradycardic syndrome, [9,32] its occurrence [illegible] most series has been unusual, if not rare N[illegible] and David[33] in reporting 74 cases of the brady[illegible]dia tachycardia syndrome noted that 51 per c[illegible] had associated coronary artery disease In t[illegible] series idiopathic' cardiac disease accounted [illegible] 34 per cent of their cases The remainder inclu[illegible] hypertension rheumatic heart disease congen[illegible] heart disease and cardiomyopathy In their se[illegible] of 21 cases of the SSS, Radford and Julia[illegible] reported one case of a patient who had ha[illegible] pericardiectomy for calcific tuberculous peric[illegible]ditis, and one case of dystrophia myotonia W[illegible] Lee and Toh [35] in a most interesting report fr[illegible] Singapore were able to document thyrotoxic[illegible] as a possible etiologic factor in six of [illegible] patients

It is obvious that iatrogenic electrocard[illegible]graphic (ECG) changes consistent with the S[illegible] are common Digitalis quinidine, procaine ami[illegible] and propranolol can all produce an ECG a[illegible] clinical picture of the SSS In some of th[illegible] patients determination of etiology may be almo[illegible] impossible, as these are the drugs used to cont[illegible] many of the presenting arrhythmias of t[illegible] syndrome It then becomes problematical whet[illegible]er the drug being used for arrhythmia manag[illegible]ment is the etiologic factor in the production [illegible] the syndrome It is precisely this puzzling situ[illegible]tion that makes therapy of the syndrome se[illegible] difficult at times Wan Lee and Toh[35] cited [illegible] patient of theirs with thioridazine hydrochl[illegible]ride-induced SSS manifested by wandering pac[illegible]maker paroxysmal atrial tachycardia and sin[illegible] arrest As will be discussed below such a ther[illegible]peutic diagnostic dilemma is often seen in cases [illegible] the bradycardia tachycardia group Propranolo[illegible] for example in use to control a supraventricul[illegible] arrhythmia, may also result in sinus bradycar[illegible]dia

In the series of cases reported by Radford and Julian[34] three siblings were included Othe[illegible]

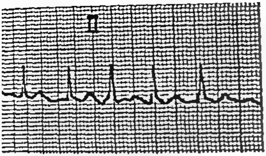

Fig 3 ECG of C P (case 2)

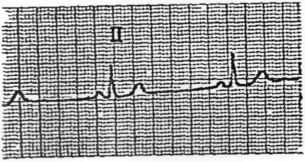

Fig 4 ECG of C P (case 2)

adherents. The circus movement theory now largely discredited postulated that a circulating ring of excitation traversed the atria. The unifocal theory postulates that the impulses of flutter and fibrillation all originate in a single ectopic center. The multiple foci and fractionate contraction theories postulate the simultaneous presence of several active pacemaking centers in the atria. Evidence for the last three theories has been cited but no firm conclusion has yet been reached regarding the actual arrhythmogenic mechanism.

As previously noted these arrhythmias are not sole evidence of the SSS. They are often associated with the brady arrhythmias however and are thus included. Initiation of a supraventricular tachycardia for example requires an ectopic atrial beat or its equivalent. This may occur from spontaneous pacemaker activity in the specialized conduction tissue of the atrium or may result from intra atrial re entry in association with asynchrony of repolarization among different myocardial fibers. In either case the likelihood of occurrence is increased at slower heart rates.

When the brady and tachy arrhythmias are associated the brady tachy syndrome a subdivision of the SSS is said to exist. Two case reports of this interesting syndrome follow.

CASE 2. C P a 62 year-old woman was admitted to the Long Island College Hospital in February 19 4 because of chest pain, palpitations and lightheadedness. About 14 years prior to admission, she was told of the presence of systemic hypertension. This had been untreated. For about 7 years, she had had intermittent palpitations but had never been bothered during such an episode. She had no associated dyspnea or chest pain but had had numerous episodes of lightheadedness for about the same length of time. The patient was unable to associate the two symptoms of palpitation and lightheadedness.

About 3 weeks prior to admission she began to complain of chest pain. This was precordial in location, oppressive radiated to the left shoulder and arm but not associated with effort. She denied diaphoresis or dyspnea during the episodes of pain.

There was no history of diabetes rheumatic heart disease orthopnea, or ankle swelling. On admission the pertinent physical findings included a blood pressure of 160/90 mm Hg. The heart rhythm was irregularly irregular but there were no murmurs, gallops, or rubs. The lungs were clear. The remainder of the physical examination was unremarkable. The following laboratory data were normal: CBC urinalysis FBS BUN PBI serum cholesterol uric acid SGOT CPK and LDH.

An ECG taken after admission showed atrial fibrillation with a ventricular response of about 130 to 140 per minute (Fig. 3) but was otherwise unremarkable. This arrhythmia continued to occur sporadically during the 7 days after admission. On several occasions the heart rhythm reverted spontaneously to sinus bradycardia at a rate of 40 to 50 (Fig 4). After attempts to control the episodes of atrial fibrillation with antiarrhythmic drugs were unsuccessful, a permanent pervenous pacemaker was inserted. The rate was adjusted to 90 per minute. In the year following insertion the patient has remained free of palpitations lightheadedness, or chest pain. Further episodes of atrial fibrillation have not been observed.

CASE 3. R. C an 81 year-old housewife was admitted to the Long Island College Hospital in April 1971 because of weakness. She had a history of diabetes mellitus for 12 years, and was taking phenformin with good control. She denied a past history of chest pain dyspnea or ankle edema but had been taking digoxin (0.25 mg. once a day) for as long as she could remember for "heart trouble." In addition quinidine sulfate (0.2 Gm. every 4 hours) had been administered for about 4 years. On previous admissions, which had been for cataract surgery and complaints of palpitations, a variety of cardiac rhythms were noted. These included sinus bradycardia, atrial fibrillation with rapid ventricular response and paroxysmal atrial tachycardia (Fig. 5). In the year prior to the present admission she had felt well however and had not been readmitted. For 1 month prior to admission, palpitations recurred and became more severe. These were associated with severe weakness and near-syncope on several occasions. The symptoms lasted from several minutes to several hours. There was never any associated chest pain or dyspnea.

On admission, the patient was noted to be in no distress

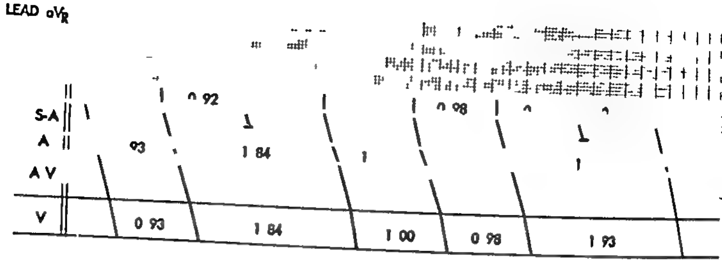

Fig 2 ECG of M C (case 1)

patient complained of lightheadedness No syncopal episodes were observed Three days after admission premature ventricular contractions were noted to be associated with the sinus bradycardia (Fig 1) A trial of propantheline failed to result in an increase in the heart rate On the thirteenth hospital day a permanent transvenous pacemaker was inserted The patient has remained free of cardiac symptoms in the 18 months following pacemaker insertion

If impulses from the sinus node are blocked at its electrophysiologic junction with the atrium sino atrial exit block is said to exist This is manifested by a bradycardia whose interval is a mathematical multiple of faster sinus intervals Simply stated an expected sinus P wave is not present and the ventricular response is not provoked (unless an escape beat occurs) (Fig 2) Electrophysiologically this is thought to result from a slowing of the exiting conduction velocity due to refractoriness of the perinodal tissues

In the case of atrial arrest or asystole a variety of electrophysiologic abnormalities may be responsible A failure of generator function of the sinus node abnormalities of perinodal conduction or atrial inexcitability may cause atrial asystole Its ECG manifestation is the sudden cessation of P waves with succeeding beats not being mathematical multiples of faster sinus rates

Atrial bradycardias are quite often not isolated arrhythmias They may indicate diffuse disease and are at times associated with blocks in the lower conduction system Narula,[11] in a study of atrial bradycardia, found that over 60 per cent of 75 patients with atrial bradycardia has other conduction disturbances These included abnormalities in the atria junctional tissues, and His Purkinje system This would seem to indicate that atrial bradycardias are usually not electrica dysfunctions which occur independently of othe arrhythmias

Atrial tachyarrhythmias Included under thi heading are sinus tachycardia paroxysmal junctional and atrial tachycardia, atrial flutter and atrial fibrillation Although these rhythms are not part of the SSS when they exist alone, they form part of the syndrome when they represen the escape mechanism for the bradycardic atria rhythms In addition chronic atrial fibrillation may be considered part of the SSS when it is due to permanent electrical silence of the sino atria node Similarly episodes of transient atrial fibrillation may occur in response to total cessation o sino atrial rhythm

In most instances sinus tachycardia result from increased slope of phase 4 depolarization A variety of chemical and mechanical factors including catecholamines and atrial stretch are involved

Supraventricular tachycardias have been intensively investigated and their mechanisms elucidated [4 11] It has been repeatedly shown that paroxysmal supraventricular tachycardia may result from sustained A V nodal re entrance That is a circulating wave front of depolarization occupies a circuit within the atria involving the A V node in a retrograde fashion thereby exciting the atria Subsequent re entry of the A V node re excites the ventricles and so on Recently it has been shown that re entrance may occur in the sino atrial node and thus be a source of supraventricular tachycardia [3]

The mechanisms of atrial flutter and fibrillation remain in dispute Four theories have had

complaints Heart rhythm was mainly pacemaker induced at a rate of 80.

Clinical picture

Age and sex There does not seem to be a sexual preponderance of the SSS In the 31 cases of Mandel, Hayakawa Allen Danzig and Kermaier [7] there were 15 women and 16 men Radford and Julian[3] reported 11 men and 10 women in the series of Rubenstein and associates, there were 25 men and 31 women Moss and Davis [33] review of 74 patients with the brady tachy syndrome included 32 men and 42 women.

In most series, the peak incidence of the SSS occurs in the seventh decade It is worth remembering, however that the syndrome does occur in children. Ferrer[49] has suggested that the SSS may explain some instances of sudden death in young athletes. One of the patients of Wan Lee and Toh [5] was 21 years old Ikeme D Arbela and Somers[34] reported a remarkable series of eight Africans with SSS All of their patients were age 32 or less and one was age 10 They did not offer any explanation for this preponderance of youthful patients

Signs and symptoms The clinical manifestations of the SSS may be quite difficult to recognize as they may be intermittent protracted and multifaceted Physiologically most signs and symptoms result from hypoperfusion of vital organs. The brain heart and kidneys are most prominently affected Moss and Davis[33] reported that 48 per cent of their patients with the brady tachy syndrome had cerebral manifestations viz syncope or near syncope and dizziness Their review of the pertinent literature however revealed that 75 per cent of the reported cases had these symptoms Forty of 56 patients reported by Rubenstein and associates had cerebral symptoms, indeed they noted 10 cerebrovascular accidents in their group An interesting association in this regard was mentioned in the *British Medical Journal* where it was observed that patients with the brady tachy syndrome are greatly at risk from systemic embolism presumably because of the changing atrial rhythms Rubenstein and associates[4] reported that eight of their 33 patients with the brady tachy syndrome had systemic embolization

Cerebral manifestations of the SSS may include such nondescript symptoms as fatigue irritability and forgetfulness It is impossible to estimate how often an elderly patient with signs and symptoms of senility may in fact have cerebral manifestations of brady or tachycardic rhythm disturbances It is incumbent on the clinician to bear in mind this possibility when investigating any patient with cerebral symptoms *of obscure origin* Of the cerebral manifestations the one with most potential hazard is syncope These cases are not included in the classical Morgagni Stokes Adams syndrome of course unless the bradycardic rhythm is complete heart block. The original report of sinus bradycardia and syncope was made by Laslett[32] in 1909 In the series of Moss and Davis [33] 25 of 74 patients had syncope Of these 65 per cent had a syncopal episode as a result of asystole following tachycardia 26 per cent due to bradycardia alone and 9 per cent due to tachycardia alone Ikeme D Arbela and Somers[34] stressed the bizarre clinical presentation of some of their patients two were thought to have psychiatric disorders and two had epileptiform fits

As would be expected the second most prominent organ producing symptoms in the SSS is the heart itself Palpitations angina and manifestations of congestive heart failure are seen as the initial symptoms in many patients In others a sudden or gradual unexplained worsening of these signs and symptoms may occur Once again a high index of suspicion is required to make a diagnosis in these cases These manifestations may result not only from tachycardia but from the failure of the heart to become tachycardic under an appropriate stimulus. In certain cases episodic and sudden unexplained episodes of pulmonary edema may be a result of the arrhythmias of the SSS Similarly mild ventricular failure can occur from persistent or episodic sinus bradycardia Angina can obviously be caused by the same mechanisms It cannot be emphasized too strongly that the arrhythmia producing these clinical signs may not be present when the patient comes under professional observation When to this problem is added the fact that other signs of heart disease may be absent in the early stages of sinus node disease diagnosis becomes particularly difficult Once again however careful and intensive investigation can result in a proper conclusion (see below) (An intriguing historical speculation in this regard was offered by Livesley [35] who attributed the cerebral symptoms and angina

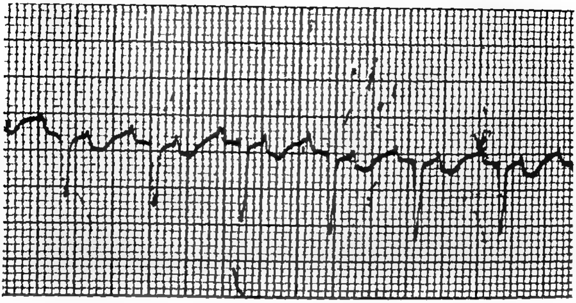

Fig 5 ECG of R C (case 3)

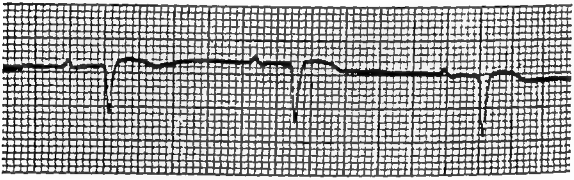

Fig 6 ECG of R C (case 3)

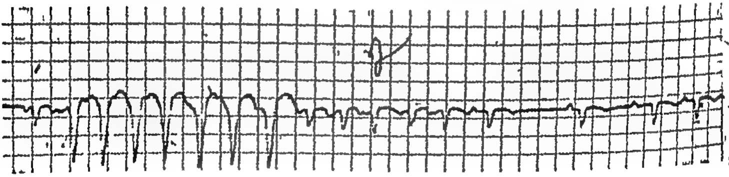

Fig 7 ECG of R C (case 3)

Vital signs were normal except for an irregular rapid pulse Pertinent physical findings were limited to the heart where atrial fibrillation was present with a ventricular response of 110 to 115 A short midsystolic Grade 2/6 systolic murmur was heard at the lower left sternal border The remainder of the physical examination was unremarkable Despite digoxin and quinidine therapy in the aforenoted dosages her cardiac rhythm varied from sinus bradycardia (Fig 6) to atrial fibrillation with a ventricular response in excess of 100 Propranolol (80 mg daily) failed to control the heart rhythm and several attempts at adjustment of digoxin and quinidine therapy failed to alter the paroxysmal atrial fibrillation or sinus bradycardia During the tachycardic episodes the patient complained of extreme weakness On one occasion a run of ventricular tachycardia was noted This terminated in supraventricular rhythm sinus arrest and sinus bradycard with wandering pacemaker (Fig 7)

About 1 month after admission a temporary perveno pacemaker was inserted and ventricular pacing initiated at rate of 85 No further episodes of brady or tachycard occurred over the next week Digoxin was continued bu quinidine was discontinued Inderal was again given in a do of 80 mg daily About 5 weeks after admission a permanen pervenous demand pacemaker was inserted The patient ha subsequently remained well and when readmitted for pac maker battery replacement 2 years later had no cardia

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Cerebral manifestations of the SSS may include such nondescript symptoms as fatigue irritability and forgetfulness It is impossible to estimate how often an elderly patient with signs and symptoms of senility may in fact have cerebral manifestations of brady or tachycardic rhythm disturbances It is incumbent on the clinician to bear in mind this possibility when investigating any patient with cerebral symptoms of obscure origin Of the cerebral manifestations the one with most potential hazard is syncope These cases are not included in the classical Morgagni Stokes Adams syndrome of course unless the bradycardic rhythm is complete heart block. The original report of sinus bradycardia and syncope was made by Laslett[5] in 1909 In the series of Moss and Davis [33] 25 of 74 patients had syncope Of these 65 per cent had a syncopal episode as a result of asystole following tachycardia 26 per cent due to bradycardia alone and 9 per cent due to tachycardia alone Ikeme D Arbela and Somers[30] stressed the bizarre clinical presentation of some of their patients two were thought to have psychiatric disorders and two had epileptiform fits

As would be expected the second most prominent organ producing symptoms in the SSS is the heart itself Palpitations angina and manifestations of congestive heart failure are seen as the initial symptoms in many patients In others a sudden or gradual unexplained worsening of these signs and symptoms may occur Once again a high index of suspicion is required to make a diagnosis in these cases These manifestations may result not only from tachycardia but from the failure of the heart to become tachycardic under an appropriate stimulus In certain cases episodic and sudden unexplained episodes of pulmonary edema may be a result of the arrhythmias of the SSS Similarly mild ventricular failure can occur from persistent or episodic sinus bradycardia Angina can obviously be caused by the same mechanisms It cannot be emphasized too strongly that the arrhythmia producing these clinical signs may not be present when the patient comes under professional observation When to this problem is added the fact that other signs of heart disease may be absent in the early stages of sinus node disease diagnosis becomes particularly difficult Once again however careful and intensive investigation can result in a proper conclusion (see below) (An intriguing historical speculation in this regard was offered by Livesley [53] who attributed the cerebral symptoms and angina

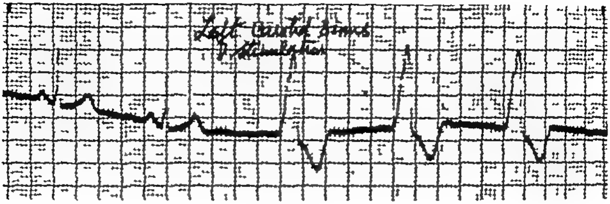

Fig 8 ECG of M P (case 4)

suffered by the famous English physician and anatomist, John Hunter to persistent and inap propriate sinus bradycardia)

ECG manifestations The most frequent single arrhythmia in the SSS is sinus bradycardia, being reported in 76 per cent of the patients of Radford and Julian [34] The series of Moss and Davis[33] had exactly the same incidence of sinus bradycardia

As noted under electrophysiology a variety of other supraventricular arrhythmias occur These have included sinus arrest junctional bradycar dia wandering atrial pacemaker supraventri cular ectopic beats intermittent sinus arrest, and sinus node exit block

As previously mentioned an inadequate sinus rate following DC cardioversion may be a sign often the initial one of SSS In like manner the use of a cardioactive drug to treat a supraventri cular arrhythmia may result in the appearance of another arrhythmia as the initial one in the diagnosis of SSS

The occurrence of ventricular arrhythmias in the SSS is unusual Only 10 per cent of the patients of Moss and Davis[33] had ventricular tachycardia or fibrillation Rubenstein and asso ciates[1] did not report any patients with ventric ular tachycardia or fibrillation in their 56 patients, and Radford and Julian[34] gave an inci dence of 8 per cent In the 10 cases of Kaplan and associates there were no ventricular arrhyth mias When such arrhythmias occur, they would seem to be an escape mechanism in response to one of the atrial bradycardic arrhythmias

The tachycardic arrhythmias of the brady tachy syndrome are mainly supraventricular and include supraventricular tachycardia and parox ysmal atrial tachycardia as the most frequent In decreasing incidence atrial flutter and fibrillation and multiple supraventricular tachy arrhythmias may be encountered

It would be expected that associated EC abnormalities in addition to arrhythmias, mig be present, and this is, indeed, the case A norm ECG does not, of course, exclude the SS Myocardial infarction is frequently encountere as are bundle branch block and ventricular hype trophy

Diagnosis

History As in all clinical medicine, the histo remains the cornerstone of diagnosis of the SS Palpitations angina, and symptoms of congesti heart failure may be an integral part of th history Sudden onset of these symptoms, or th aggravation of a previously stable clinical cond tion, may point to the proper diagnosis Whe syncope is the presenting symptom, a broade diagnostic investigation is indicated, includin metabolic and neurologic disorders When the are excluded however a search for the SSS ma be indicated, particularly in the presence cardiac symptoms It should be mentioned tha the patient with syncope of cardiac origin usuall has episodes that are sudden brief, and leave few if any sequelae Associated cerebrovascula disease may of course alter the presentation

The clinician should carefully question th patient with syncope regarding any cardiac symp toms On occasion a history of palpitation will b elicited, and, may be noted by the patient t immediately precede the syncopal episode

The fact that cardioactive drugs such as quin idine and procaine amide may expose a previousl unsuspected sick sinus cannot be too strongly emphasized In a not unusual sequence a patient is given one of these drugs to control a tachy cardic rhythm and responds with an episode of prolonged sinus arrest or asystole

Physical examination Aside from a resting heart rate that may be below 60, or the detection

of an arrhythmia physical findings are usually of little help in establishing the diagnosis of the SSS.

ECG This, of course is the final parameter of diagnostic investigation In detection of the SSS several methods have been employed

Ambulatory (Holter) ECG tape monitoring has greatly advanced the diagnosis of cardiac arrhythmias The episodic brady or tachycardias of the SSS may be documented by this method and it is particularly valuable in the case where routine electrocardiography is not fortuitously performed during an arrhythmia Occasionally arrhythmias are recorded even in the absence of symptoms but are of course diagnostic when symptoms and arrhythmia concur Although many arrhythmias will be documented in a 12 hour recording the more recent availability of totally portable 24 hour monitoring systems makes prolonged surveillance easier Consequently the longer period of recording is indicated in almost all cases It is worth emphasizing that the bradycardic aspects of the syndrome may be detectable only during sleep This makes a 24 hour recording almost mandatory Ferrer[4] mentioned a patient with a sleeping rate of 28 beats per minute whereas the rate during the day was 50.

Provocative tests

Carotid sinus massage This has been advocated as a provocative test for the SSS The response to this maneuver which should be done only with ECG monitoring is difficult to interpret at times. Ajuiss Rosin and Adolph have reported that significant sinus slowing may occur in elderly persons with sinus bradycardia who are asymptomatic In his series of 31 cases of the SSS however Mandel [7] reported seven with an abrupt sinus arrest lasting longer than 3 seconds In four this response was the major manifestation of sinus node disease

A pause longer than 3 seconds with carotid sinus massage is highly suggestive of inappropriate sinus node responsiveness and sinus node disease. Such a response should at least alert the physician and warrants further investigation Besides this response however we have noted that an escape rhythm may supervene when carotid sinus pressure is applied

CASE 4. M [illegible] a 51 year-old white male house painter was admitted to the Long Island College Hospital in October 1973, because of syncope About 4 months before he had been admitted because of transient left hemiplegia and slurring of speech. His symptoms gradually regressed and an ECG showed inferior wall myocardial ischemia and an old anteroseptal myocardial infarction He also stated that he had had episodic retrosternal pain with effort or emotion

In the 3 or 4 weeks before admission he began to have near syncopal episodes. These lasted a few minutes, occurred without warning, and were without sequelae Although he never lost consciousness, the patient described extreme weakness and lightheadedness during these episodes. Carotid sinus pressure in his private physician s office resulted in a similar episode and was associated with a period of asystole lasting about 3 seconds. Physical examination was unremarkable on admission and an ECG showed sinus rhythm and a probable old anteroseptal myocardial infarction A rhythm strip during massage of the left carotid sinus showed conversion of a sinus bradycardia to an idioventricular rhythm (Fig 6) A permanent pervenous pacemaker was subsequently inserted. The patient has remained free of syncopal attacks since

COMMENT In retrospect it would seem that the episode of cerebrovascular insufficiency on the first admission was in fact related to an arrhythmia of the SSS

Valsalva maneuver This may also be employed to demonstrate sinus node dysfunction Further it may be used to distinguish the SSS from physiologic sinus bradycardia of the elderly In the latter situation the increase in heart rate during the strain phase (phase II) occurs as does subsequent slowing of the heart rate during the blood pressure overshoot (phase IV) In patients with the SSS the blood pressure responses to Valsalva maneuver occur but there is little or no change in pulse rate Once again however this procedure is not diagnostic of sinus node disease but may be used as confirmatory evidence and as the stimulus for further investigation

Atropine administration The intravenous administration of atropine may exclude the SSS This drug will reveal the vagal etiology of sinus bradycardia by eliminating it Ferrer[4] has stated that if intravenous atropine sulfate (1 to 2 mg) does not increase sinus bradycardia to a sinus rate exceeding 90 per minute and if after atropine sinus node recovery time remains prolonged after overdrive (see below) the diagnosis of a failing SA node is made Rosen Loeb Senno Rahimtoola and Gunnar[15] reported the response to intravenous atropine of 11 patients with apparent sinus node disease Although eight were considered responsive to the drug with 25 to 125 per cent increase in heart rate no patient developed a sinus rate greater than 90 beats per minute An interesting associated finding in this series was that all patients receiving atropine developed

facilitation of A V conduction with shortening of PR and PH intervals Also in two patients, the sinus node response to atropine was considered 'sluggish,' in that junctional foci accelerated prior to the increase in sinus rate

Atrial pacing This is considered by most authorities to be the most valuable provocative test in the SSS

Atrial pacing in the sick sinus syndrome is generally performed by the placement of a pacing catheter in the right atrium at the right atrial-superior vena caval junction or within the coronary sinus Reliable pacing is maintained with minimum current, and is begun at 90 beats per minute The pacing rate is then increased by 10 beat increments to 150 beats per minute Each pacing period is of 2 minutes duration At the end of each period pacing is abruptly terminated and the interval from the last pacing stimulus to the onset of the next P wave is measured If atrial asystole occurs the interval to the junctional escape beat is used This represents the sinus node recovery time Narula Samet and Javier[38] however introduced the concept of the corrected sinus node recovery time (CSRT) as being a more accurate assessment of sinus node function The CSRT is defined as the difference between the recovery interval following tachypacing and the average resting P P interval Although sinus node suppression may be found after atrial pacing of the normal heart it is related to the resting or control sinus rate, with slower control rates being associated with longer maximum pauses

In the heart with a diseased or malfunctioning sinus node, the CSRT will be prolonged to a greater degree then normal Ferrer[49] felt that the degree of overdrive suppression is best expressed as a percentage of the control rate In her view at a resting rate of 75 to 85 beats per minute the maximum pause is between 115 and 128 per cent of the control cycle length (or pauses of 800 to 900 msec) With a control rhythm of sinus bradycardia at a rate of 45 to 60 pauses of 1 200 to 1,400 msec duration represents the critical figure beyond which abnormal suppression is diagnosed At control rates of 60 beats per minute a pause of 125 per cent of control (1,250 msec) is strongly suggestive of SSS If a sinus bradycardia of 45 beats per minute is the control rhythm, a pause of 1,700 msec or more is diagnostic even though the percentage increase is 120 per cent

In their study of 46 patients, Mandel, Hayakawa, Danzig, and Marcus[41] evaluated SA node function in 46 patients, three of whom had the SSS They found a CSRT of 1 041 ± 56 msec in the normal patients and 4,732 ± 415 msec in those with the SSS In another series of patients with SSS, Mandel and associates[47] found a mean maximum postpacing CSRT of 3,164 ± 334 msec in 29 In this series, they considered a normal SCRT to be 1,073 ± 67 msec

Although atrial pacing is frequently used as a diagnostic aid in the SSS, false negatives may occur This may be seen because of SA node entrance block, as an adequate challenge by SA node overdrive is based on the assumption that all of the rapid atrial depolarizations enter the SA node If entrance block exists, the SA node will be challenged by a smaller number of paced beats than the atrial myocardium

In contrast to the aforementioned studies, Gupta, Lichstein Chadda, and Badin reported sinus node recovery time in 17 patients with the SSS compared with 15 controls In the 15 control subjects the CSRT ranged from 0 to 375 msec In 17 patients with the SSS, the CSRT was normal in 11 (150 to 350 msec) and prolonged in only six (480 to 5 690 msec) They recommend repetition of atrial pacing after the intravenous administration of atropine to elicit an abnormal response in patients with a normal CSRT and the SSS

In their series of seven patients with SSS who underwent repeat atrial pacing after atropine administration, four had no significant change in CSRT but three had junctional escape rhythm following cessation of atrial pacing A similar effect was noted by Narula Samet and Javier[38] in four of 10 patients with SSS studied after atropine Bashour, Hemb, and Wickramesekaran[48] noted the same phenomenon

In summary although atrial tachypacing remains a valuable diagnostic tool in SSS false negative responses occur The physician should be alert for these and proceed to other investigative procedures including atropine administration, where indicated

Therapy

The therapeutic dilemma facing the physician treating the SSS by pharmacologic means has already been alluded to viz the agent used to treat one extreme of arrhythmia may precipitate the other extreme The classical example is the use of atropine or isoproterenol to treat a brady

cardic rhythm with resulting tachycardia It is this dilemma that has resulted since 1966 in the increased use of the permanent artificial pacemaker to treat the SSS

Before therapy is instituted however it must be first decided which patient is in need of treatment. In their excellent article on the brady tachy syndrome Moss and Davis[13] suggested that patients requiring therapy be divided into those with major or minor symptoms The major category includes cerebral, coronary or low output problems. The minor categories include mild ankle edema, subjective palpitations and an uncomfortable awareness of slow rapid, or irregular heartbeat Although the major symptoms require therapy of a more intense nature the patient with only minor symptoms may be managed with low dose diuretics reassurance and anxiety reducing medications

Obviously asymptomatic arrhythmias of life threatening potential should be vigorously and immediately treated as follows

Pacemaker therapy remains the foundation of treatment for the symptomatic patient Drugs such as atropine usually are either ineffective or productive of intolerable side effects Both atrial and ventricular pacing have been used and their efficacy repeatedly demonstrated

In the absence of A V conduction disturbances atrial pacing should be considered because of its advantages of maintenance of normal electrophysiologic conduction pathways and preservation of atrial transport function It should also be remembered that atrial pacing may prevent the inhibition of atrial tachyarrhythmias by overdrive The suitability of atrial pacing however is dependent upon the normalcy of A V conduction and this can be determined accurately only with His bundle recording In institutions which do not have the capability of this technique evaluation of A V conduction can also be carried out by atrial tachypacing [7,14] If the PR interval remains less than 0 22 second during atrial tachypacing at rates of 120 to 140 per minute permanent atrial pacing can be safely performed If however A V block is clinically evident or is elicited with atrial tachypacing or in the presence of bifascicular conduction disturbances ventricular pacing is the therapy of choice The significant incidence of A V conduction disturbances in the SSS must be constantly recalled in these considerations Rosen and associates found that 53 per cent of their patients with SSS had such a disturbance

Thus in most cases of SSS permanent ventricular pacing remains the therapy of choice This approach is of obvious value in reduction of symptoms due to bradycardia The accompanying atrial tachyarrhythmias however are rarely controlled by this method alone Such control may occur if ventriculoatrial conduction is present and the atrial depolarization following each paced ventricular beat suppresses ectopic atrial rhythms In the absence of such a fortuitous set of circumstances however other therapy to suppress ectopic atrial rhythms must be sought Pharmacologic therapy is the usual choice Ventricular pacing will allow the use of certain drugs such as propranolol without concern for the bradycardic effects of such agents Similarly quinidine procaineamide or digitalis can be administered without the danger of further bradycardia

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REFERENCES

1 Rubenstein J Schulman C Yurchak P and DeSanctis R Clinical spectrum of the sick sinus syndrome Circulation 46 5 1972
2 Kaplan, B Langendorf R Lev M and Pick, A Tachycardia bradycardia syndrome (so called sick sinus syndrome) Am J Cardiol 31 497 1973
3 Birchfield R I Menefee, E E and Bryant G D N Disease of the sino-atrial node associated with bradycardia asystole syncope and paroxysmal atrial fibrillation Circulation 16 20 1957
4 Vouvram, Y Slama R and Temkine J Le bloc sino auriculaire et les maladies du sinus Reflexions à propos de 63 observations Arch. Mal Coeur 60 153 1967
5 Miller O F Finkelstein D Adams-Stokes syndrome due to sinoatrial block, Am J Cardiol 17 433 1966
6 DeZorday I Unusual features of two cases of sino-auricular block Am Heart J 12 339 1936
7 Winton S S Sino auricular block An analysis of eleven cases, Acta Cardiol. 3 108 1948
8 Short, D S The syndrome of alternating bradycardia and tachycardia Br Heart J 16 208 1954
9 Lown, B Electrical reversion of cardiac arrhythmias Br Heart J 29 469 1967
10 Ferrer M I The sick sinus syndrome in atrial disease J A M.A. 206 645 1968
11 Silverman L F Mankin, H T and McGoon D C Surgical treatment of an inadequate sinus mechanism by implantation of a right atrial pacemaker electrode J Thorac Cardiovasc Surg 55 264 1968
12 Tolatznik, B Mower M M., Somson E B and Prempree A Syncope in the sluggish sinus node syndrome Circulation 40 (Suppl. III) III 200 1969

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Present state of alpha- and beta-adrenergic drugs I The adrenergic receptor

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The increasing clinical use of the beta adrenergic receptor blocking agents such as propranolol has stimulated interest in the entire spectrum of adrenergic drugs In a series of three articles this whole field will be examined and reviewed The first part will consider the receptor and its agonists The second will cover the general aspects of adrenergic blockade The third section will consider the beta blocking agents in some detail.

The adrenergic receptor is the site of action of norepinephrine the neurotransmitter of sympathetic adrenergic nerves Located on the effector cell (muscle or gland) the adrenergic receptor is also the site of action of epinephrine the principal hormone of the human adrenal medulla In addition, the receptor is acted on by a multitude of drugs related structurally to the natural catecholamines. Not all receptors are associated with innervated effectors Some appear to be naked That is there is no nerve that can be stimulated to evoke their response The receptors of the nutrient blood vessels in skeletal muscle appear to be of this type

The function of the adrenergic receptor is to detect and interact with the transmitter This interaction triggers some characteristic response of the effector cell The basic interaction between the agonist and the receptor is probably a conformational change in some part of the cell membrane Some evidence for this is (1) the receptor responds best to a favorite chemical structure epinephrine and (2) it prefers left handed (levorotatory) molecules It is postulated that the triggering mechanism involves adenyl cyclase and cyclic AMP However for our purposes the exact mechanism of this step is unimportant

The important cardiovascular responses controlled by adrenergic receptors are (1) increased sinus heart rate (positive chronotropic action) (2) increased force of myocardial contraction (positive inotropic action) (3) increased rate of conduction within the A V system (4) vasoconstriction of almost all blood vessels and (5) vasodilation of nutrient blood vessels

Dale in 1906 described what he called the receptive mechanism for adrenaline He used this concept at the time to explain the actions of the ergot alkaloids However he apparently never again considered receptors Cannon and Rosenblueth[2] evoked an adrenergic receptor in their theory of the two sympathins E and I In their view the receptor was a tissue component that joined with epinephrine from the nerve end to form sympathin The idea of sympathin E (excitatory) and sympathin I (inhibitory) has not survived

In 1948 we[3] [4] published the results of a comparative study of five catecholamines These amines were those most closely related to epinephrine and included isoproterenol norepinephrine cobefrine epinephrine and methylepinephrine Their activities were compared on a variety of isolated tissues and intact animal systems It was found that only two orders of activity were found On one set of responses epinephrine was the most potent with isoproterenol the least potent On the other set of responses isoproterenol was the most potent and norepinephrine the least potent

The only way that the results could be explained was to assume that there are at least two different kinds of adrenergic receptor One we called alpha the other beta According to this concept the adrenergic cardiovascular responses

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13 Easley R M and Goldstein S Sino atrial syncope Am J Med 50 166 1971
14 Schulman C L Rubenstein J J Yurchak P N and DeSanctis [redacted] W The sick sinus syndrome Clinical spectrum Circulation 42 (Suppl III) III-42 1970
15 Keith A and Flack M Form and nature of the muscular connections between the primary divisions of the vertebrate heart J Anat Physiol 41 172 1907
16 Wybouw R Sur le point d origine de la systole cardiaque dans l oreillette droite, Arch Intern Physiol Biochim 10 78 1910
17 Lewis T Oppenheimer [redacted] S and Oppenheimer A Site of origin of the mammalian heart beat The pacemaker in the dog Heart 2 147 1910
18 Walmsley T Comparative anatomy of the heart *in* Quain s Elements of anatomy part *III* vol 4
19 James T N Pericarditis and the sinus node Arch Intern Med 110 305 1962
20 James T N Anatomy of the coronary arteries New York 1961 Hoeber Medical Division of Harper & Rowe Publishers Inc
21 Soderstrom U Myocardial infarction and mural thrombosis in the atria of the heart Acta Med Scand 132 (Supp 217) 114 1948
22 James T N and Nadeau R A Sinus bradycardia during injections directly into the sinus node artery Am J Physiol 204 9 1963
23 James T N and Nadeau R A Relation of retrograde pressure in the sinus node artery to sinus tachycardia from stellate stimulation J Lab Clin Med 62 777 1963
24 Harary I Heart cells in vitro Sci Am 206 141 1962
[redacted] Hoffman B F and Cranefield P F Electrophysiology of the heart New York 1961 McGraw Hill Book Company Inc
[redacted] Cohn A E and Lewis T Auricular fibrillation and complete heart block A description of a case of Adams Stokes syndrome including the postmortem examination Heart 4 15 1912 1913
27 Rasmussen K Chronic sino atrial heart block Am Heart J [redacted] 38 1971
28 Allensworth D C Rice G J and Lowe G N Persistent atrial standstill in a family with myocardial disease Am J Med 47 775 1969
29 Kirk J E and Kvorning [redacted] A Sinus bradycardia A clinical study of 515 consecutive cases Acta Med Scand Suppl 266 625 1952
30 Primary myocardial disease I Clinical features Ann Intern Med 58 426 1963
31 Massumi R A Rios J C Gooch A S Mutter D DeVita V T and Datlow D N Primary myocardial disease Report of 50 cases and review of the subject Circulation 31 19 1965
32 Hamby R I and Raia F Electrocardiographic aspects of primary myocardial disease in 60 patients Am Heart J 76 316 1968
33 Moss A J and Davis R J Brady tachy syndrome Prog Cardiovasc Dis 16 439 1974
34 Radford D J and Julian D G Sick sinus syndrome Experience of a cardiac pacemaker clinic Br Med J 3 504 1974
35 Wan S, Lee G S and Toh C The sick sinus syndrome A study of 15 cases Br Heart J 34 942 1972
36 Sarachek, U S and Leonard J J Familial heart block and sinus bradycardia Classifications and natural history Am J Cardiol 29 451 1972
37 Spellberg [redacted] D Familial sinus node disease Cl 60 246 1971
38 Gambetta M Weese J Ginsburg [redacted] and Shapiro Sick sinus syndrome in a patient with familial prolongation Chest [redacted] 520 1973
39 Rokseth, R. and Hatte L Sinus arrest in acute myo dial infarction Br Heart J [redacted] 639 1971
40 James T N The coronary circulation and conduct in acute myocardial infarction Prog Cardiovasc 10 410 1968
41 Narula O [redacted] Atrioventricular conduction defects patients with sinus bradycardia Circulation 44 1971
42 Wallace A G and Dagget W M Re-excitation of atrium—the echo phenomenon Am Heart J 68 1964
43 Gettes L W and Yoshonis K F Rapidly recurr supraventricular tachycardia Circulation 41 689 19
44 Wit A L Goldreyer [redacted] N and Damato A N A vitro model of paroxysmal supraventricular tachycar Circulation 43 862 1971
45 Wu D Amat y Leon F Denes, P Dhingra [redacted] Pietras R J and Rosen K M Demonstration sustained sinus and atrial re entry as a mechanism paroxysmal supraventricular tachycardia Circulat 51 234 1975
46 Goel B G and Hou J Atrial ectopic activity as ciated with sinus bradycardia Circulation 42 803 19
47 Mandel W J., Hayakawa H Allen, H N Danzig and Kermaier A I Assessment of sinus node functio patients with the sick sinus syndrome Circulati 46 761 1972
48 James T N Congenital deafness and cardiac arrhy mias Am J Cardiol 19 627 1967
49 Ferrer M I The sick sinus syndrome Circulati 47 635 1973
50 Ikeme A C D Arbela P G and Somers K The si sinus syndrome in Africans Am Heart J 89 2 1975
51 Editorial The sick sinus syndrome Br Med J 2 6 1973
52 Laslett E E Syncopal attacks associated wi prolonged arrest of the whole heart Q J Med 2 3 1909
53 Livesley [redacted] The spasms of John Hunter A new inte pretation Med Hist 17 70 1973
54 Ajuiss, N S Rosin E Y and Adolph R J Significan of chronic sinus bradycardia in elderly people Circul tion 46 924 1972
55 Rosen, K M Loeb H. S Senno M Z Rahimtool S H and Gunnar R [redacted] Cardiac conduction in patien with symptomatic sinus node disease Circulation 43 83 1971
56 Narula O S Samet P and Javier R P Significance the sinus node recovery time Circulation 45 140 19
57 Mandel W Hayakawa H Danzig R and Marcu H S Evaluation of sino atrial node function in man overdrive suppression Circulation 44 59 1971
58 Gupta P [redacted] Lichstein E Chadda K D and Badin E Appraisal of sinus nodal recovery time in patients wit sick sinus syndrome Am J Cardiol 34 265 1974
59 Bashour T Hemb [redacted] and Wickramesekaran R A unusual effect of atropine on overdrive suppressio Circulation 48 911 1973
60 Rokseth P Gedde Dahl D and Foss P O Pacemake therapy in sino atrial block complicated by paroxysma tachycardia Br Heart J 32 93 1970

Isoproterenol (isoprenaline) is the specific beta receptor agonist This catecholamine produces an increase in heart rate myocardial contraction and atrioventricular conduction velocity Isoproterenol also produced vasodilation This is greatest in skeletal muscle and least in the kidney Isoproterenol is a well established drug in cardiology However as with any other drug there are still disagreements as to its actions and uses in specific patients For example which is better in cardiogenic shock norepinephrine or isoproterenol? Both stimulate the myocardium But norepinephrine increases the peripheral resistance while isoproterenol decreases resistance

Epinephrine is the second most potent beta agonist. Its use however is limited by its strong vasoconstricting action through alpha receptors Vasoconstrictors are commonly added to local anesthetic solutions In this regard epinephrine is the most potent followed by norepinephrine and phenylephrine Care must be taken when epinephrine is injected into areas having only alpha receptors For example gangrene can be produced in the toes Norepinephrine also acts on beta receptors but this action is obscured by its alpha action

Each adrenergic receptor and its associated effector cell has a unique dose-response relationship This means that it is possible to have agonists that are selective in their action Terbutaline is a selective agonist acting primarily on the beta receptors of smooth muscle When used to treat bronchial asthma terbutaline has only a slight action on cardiac beta receptors This is in contrast to isoproterenol whose antiasthmatic action may be complicated by excessive myocardial stimulation

A third category of adrenergic agonists include the indirect agents such as mephentermine the false transmitter producers like metaraminol the partial agonists such as ethylnorepinephrine and the mixed function substances exemplified by dopamine

Mephentermine acts by displacing the norepinephrine stored in the granules in adrenergic nerve ends. This drug requires an intact nerve end in order to show its pharmacodynamic effect Chronic adrenergic denervation either surgical or chemical interferes with its action On administration the cardiovascular effects are cardiac stimulation and vasoconstriction

Metaraminol acts partly indirectly by displacing norepinephrine from nerve ends It also acts directly on alpha receptors And finally metaraminol replaces norepinephrine in the nerve end enters the storage mechanism and then functions as a false transmitter When administered intravenously it acts basically as a pressor agent However on stopping long term infusion the adrenergic nerves natural function is impaired

Ethylnorepinephrine is a beta agonist used as an antiasthmatic However its action is so complex it is difficult to understand how it can be used clinically In experimental animals at least repetitive administration shows it to be a beta blocking agent and an alpha agonist The following illustrates these effects The first intravenous dose of ethylnorepinephrine produces a depressor response As this dose is repeated the depressor response vanishes and is replaced by a pressor response These effects could occur in a patient with severe asthma using frequent doses of ethylnorepinephrine

Dopamine is a complex agent It increases contractility stroke volume and cardiac output by acting on beta receptors of the heart In high dosage dopamine produces vasoconstriction by acting on alpha receptors In low and moderate doses it increases renal blood flow by acting on specific dopaminergic receptors However at high doses renal vasoconstriction will appear From a clinical standpoint the adverse effects of dopamine are identical to those of norepinephrine the adverse effects are due to alpha receptor activation

Summary

The cardiovascular alpha adrenergic receptors evoke vasoconstriction; the cardiovascular beta receptors evoke vasodilation and cardiac stimulation All blood vessels have both alpha and beta receptors In some areas for example skin and kidney the alpha receptors predominate In some vascular beds for example the nutrient vessels in skeletal muscle beta receptors predominate In other beds such as coronary visceral and connective tissue both receptors are active

The cardiovascular effects of adrenergic agonists depend on which receptor they act on Phenylephrine is specific for alpha receptors Isoproterenol is specific for beta receptors Epinephrine and norepinephrine act on both

The real value of knowing the receptor specificity of each agonist is that side effects can more

Table I Adrenergic drugs

A *Alpha receptor agonists*	
Epinephrine (1)*	
Levarterenol (norepinephrine) (Levophed) (10)	
Phenylephrine (Neo Synephrine) (25)	
Methoxamine (Vasoxyl) (25)	
B *Beta receptor agonists*	
Isoproterenol (Isuprel) (1)	
Epinephrine (2)	
Norepinephrine (25)	
Terbutaline (100)	
C *Miscellaneous*	
Mephentermine (Wyamine)	
Metaraminol (Aramine)	
Ethylnorepinephrine (Butanephrine)	
Dopamine	

*Refers to potency For example epinephrine is the most potent alpha agonist (1) epinephrine is about half (2) as potent as isoproterenol

are (1) vasoconstriction through alpha receptors and (2) cardiac stimulation and vasodilation through beta receptors

Our dual receptor concept was more or less ignored in the United States However it was well accepted abroad and many confirmatory papers appeared It was not until a specific blocking agent for the beta receptor was found that the dual receptor concept became generally acceptable and clinically useful

The classical sympathetic blocking agents such as the ergot alkaloids and yohimbine were found to act mainly on the alpha receptor The discovery by Nickerson[6] of dibenamine an absolutely specific alpha blocking agent initiated a search for more and better alpha blockers

Table I lists some clinically useful agonists It demonstrates that epinephrine is the most potent agonist when both receptors are considered As is well known, the administrator of this catechol amine evokes all adrenergic cardiovascular responses This leads to a confusing manifestation of action An intravenous infusion can produce tachycardia, increased pulse pressure increased cardiac output a decrease in total peripheral resistance, a decrease in diastolic pressure and intense cutaneous and renal vasoconstriction The exact response depends on the control conditions

It is not the purpose of this series to detail the clinical uses of adrenergic drugs since with the possible exception of the beta receptor blocking agents these are well known Rather it is our purpose to describe these drugs in terms of modern adrenergic receptor theory This shou make it easier to understand the clinical action uses, interactions and precautions

Norepinephrine, when administered as a pre sor agent, gives the appearance of acting only alpha receptors Peripheral resistance and dia tolic pressure are increased the mean arteri pressure increases causing a reflex bradycardi and the skin shows vasoconstriction The ren blood flow decreases markedly All of these a alpha effects Norepinephrine however, does a on beta receptors since this catecholamine is th adrenergic transmitter It is only when it administered exogenously that the alpha effe predominates

Phenylephrine is a specific alpha agonist I cardiovascular effects are obvious Generalize vasoconstriction resulting in a pressor respon with reflex bradycardia results from any form parenteral administration A comparison wit norepinephrine can be illustrated by the dru concentration in the intravenous infusate Fo levarterenol this is 2 mg of base in 500 ml dextrose 5 per cent, for phenylephrine this is 1 mg in 500 ml Phenylephrine can be administere subcutaneously intramuscularly or intravenou ly Norepinephrine can be administered onl intravenously If norepinephrine escapes into th perivenous tissue a permanent alpha recepto mediated vasoconstriction is the result This leads to tissue necrosis and sloughing This acciden can be treated by local administration of an alpha blocking agent such as phentolamine

In ordinary clinical usage phenylephrine has no direct adrenergic action on the heart Phenyleph rine bradycardia is a reflex effect due to the rise in pressure Therefore, no rise in arterial pressure no bradycardia Under certain conditions phenyl ephrine can induce ventricular arrhythmias For example in a hypotensive state there may be excessive reflex sympathetic cardiac stimulation The reflex vagal stimulation evoked by phenyl ephrine as it raises the pressure can produce a transient heart block This allows the ventricle to show a sympathetic induced arrhythmia

The actions and uses of methoxamine are similar to those of phenylephrine Of historical interest is a paper by Levy and Ahlquist in which it was hinted that methoxamine could block beta receptors especially those of blood vessels This finding was made before beta blocking agents were discovered

Reevaluation of the prognosis of patients with LAD–RBBB

The prognosis of patients with left axis deviation (LAD) and complete right bundle branch block (RBBB) has not yet been fully delineated outside the setting of acute myocardial infarction.

This electrocardiographic entity is generally attributed to a primary sclerodegenerative disease of the conducting system. It is known to accompany widely spread lesions of both bundle branches and to represent a frequent forerunner of complete atrioventricular block.

The incidence of complete heart block in this group of patients has been reported at 6 per cent by Lenègre, 6 per cent by Rosenbaum and associates, and 10 per cent by Lasser and colleagues. None of these authors however specified the duration of follow up in their series. Later studies indicated that the incidence of heart block increases when longer periods of follow up are available. Thus, during follow up periods of 13 months, 19 months, and 58 months, Watt and Pruitt, Scanlon and associates, and our group observed the development of complete A V block in 9 per cent, 13 6 per cent and 2 per cent, respectively. This feature prompted us to assess the risk of complete A V block as a function of the duration of follow-up after recognition of the bilateral conduction disturbance. From a review of 38 patients showing LAD RBBB and clinically devoid of any symptom suggesting transient episodes of paroxysmal A V block, it was shown that the expected incidence of the latter complication could be estimated at about 6 per cent per year of follow up after recognition of LAD-RBBB. A similar figure was recently obtained in a prospective study by Denes and co-workers (6 per cent of occurrence of A V block during a mean follow up period of 1 1⁄2 years). Although none of our patients had syncope or dizziness at the time of their initial admission it has to be stressed that they were all selected from a review of hospital electrocardiograms. This, of course introduces an element of preselection. The present annotation reports the preliminary results of a prospective study based on a population of individuals detected by the mobile screening units which the Provincial Government of the Province of Liège created in 1972.

In various villages or cities of the Province all citizens aged 50 or over are urged to submit themselves to a cardiovascular check up. They fill out a health history questionnaire and have their height, weight and blood pressure carefully measured. An electrocardiogram and a chest X Ray are also taken. Whenever it is considered necessary by the physicians in charge of the programme the patients are sent to their family doctor for further examination and/or treatment. About 15 per cent of the whole population are thus examined.

In the first 20 000 tracings, the incidence of the main types of intraventricular conduction defects was as indicated in Fig 1. The over all incidence of LAD RBBB was 35 per cent with a much higher frequency in men (6 per cent) than in women (1 per cent).

In order to evaluate further the magnitude of the risk of developing complete heart block in patients with this syndrome we reviewed in June 1975 all the patients who were detected to have LAD RBBB before September 1 1973.

Table I Patients with RBBB–LAD Age distribution and clinical data

	Total	Male	Female
Age (years)			
50-59	9	5	4
60-69	17	8	9
70-79	19	13	6
80 or over	1	–	1
Total	46	26 (57 %)	20 (43 %)
Hypertension	26 (57 %)	10 (38 %)	16 (80 %)
Angina	11 (24 %)	5 (19 %)	[illegible] (30 %)
Cardiomegaly (x Ray)	10 (22 %)	5 (19 %)	5 (25 %)
Marked dilatation of the aortic root with calcifications	7 (15 %)	4 (15 %)	3 (15 %)
Chronic pulmonary disease	1 (2 %)	1 (4 %)	–

There were 46 such patients 26 male and 20 female. The age distribution as well as the main clinical data at the time of the screening examination are summarized in Table I. Hypertension and ischemic heart disease were frequent especially in women. Associated conduction and rhythm disturbances were much less common (sinus bradycardia 5 cases, ventricular premature beats 4 cases, prolonged P R interval, 2 cases, sino-atrial block 1 case). No patient was lost to follow up. The duration of this follow up varied from [illegible] to 28.5 months with an average of 24 7 months. During this period only one patient died in hospital from cerebrovascular hemorrhage. None of the others developed complete heart block or presented with symptoms of transient atrioventricular transmission disturbances (dizziness, syncope).

Had the figures obtained in our 1973 paper been valid in this group we should have expected at least 5 or 6 cases of development of complete A V block, a prevision which was not confirmed.

easily be predicted For example, adrenergic cardiac stimulants are antiasthmatics Therefore adrenergic antiasthmatics can produce excessive cardiac stimulation

For the future, agonists that are not only receptor specific but also tissue specific will be developed The first of these in the United States is terbutaline The rest of the world has in addition a similar drug, salbutamol No one knows if this drug will be approved for use by American physicians

REFERENCES

1 Dale H H On some physiological actions of ergot J Physiol (Lond) 34 163 1906
2 Cannon W B and Rosenblueth A Studies on conditions of activity in endocrine organs XXIX Sympathin E and Sympathin I Am J Physiol 104 557 1933
3 Ahlquist R P A study of the adrenotropic receptors Am J Physiol 153 586 1948
4 Ahlquist R P Adrenergic receptors a personal a practical view Perspect Biol Med 17 119 1973
5 Levy B and Ahlquist R P Adrenergic drugs DiPalma J R editor Drill s Pharmacology in Medicine New York 1971 McGraw Hill Book Company Inc pp 627
6 Nickerson M and Goodman L S Pharmacological properties of a new adrenergic blocking agent N dibenzl β chloroethylamine (Dibenamine) J Pharmacol Exp Ther 89 167 1947
7 Levy B and Ahlquist R P Inhibition of the adrenergic depressor response J Pharmacol Exp Ther 121 4 1957
8 Ahlquist R P Isoproterenol in cardiology Am Heart J 86 149 1973

9. Kulbertus, H and Collignon P Association of right bundle branch block with left superior and inferior intraventricular block. Its relation to complete heart block and Adams Stokes syndrome Br Heart J 31 435 1969.
10. Scanlon, P J Pryor R and Blount S G., Jr Right bundle branch block associated with left superior or inferior intraventricular block Clinical setting Prognosis and relation to complete heart block, Circulation 42 1123, 1970
11. Kulbertus, H E The magnitude of risk of developing complete heart block in patients with LAD RBBB Am Heart J 86 278 1973
12. Denes, P Dhingra R C Wu D Chuquimia R Amat y Leon, F Wyndham, C and Rosen K M H V interval in patients with bifascicular block (right bundle branch block and left anterior hemiblock) Clinical electrocardiographic and electrophysiologic correlations, Am. J Cardiol. 35 23, 1975
13. DePasquale N P and Bruno M S Natural history of combined right bundle branch block and left hemiblock (Bilateral Bundle Branch Block) Am. J Med 54 297 1973.
14. Lauresse A Singson C and Alexander S Prognosis of right bundle branch block and marked left axis deviation Am J Cardiol (Abstract) 31 143 1973
15. Kulbertus, H de Leval Rutten F and Demoulin J C Electrophysiologic findings in patients with documented transient second degree or complete heart block (In preparation)
16. Puech, P Atrioventricular block The value of intracardiac recordings in Krikler D M., and Goodwin J F., editors Cardiac arrhythmias. The modern electrophysiological approach London 1975 W B Saunders Co., Ltd p 81
17. Scheinman, M M Brennan, M., Modin G., and Peters, R. Cooperative prospective study of bundle branch block Circulation 51 and 52 (Suppl. II) 444 1975
18. Denes, P Dhingra R Wu D Amat y Leon F., Wyndham C R C and Rosen K Sudden death in patients with chronic bifascicular block Circulation 51 and 52 (Suppl II) 442 1975
19. McAnulty J Kauffman, S., Murphy E., O Connell M., Kassebaum D and Rahimtoola S Survival of patients with conduction system disease Circulation 51 and 52 (Suppl. II) 443, 1975
20. Herbert, W H Left bundle branch block and coronary artery disease J Electrocardiol. 8 317 1975

Prevention and early recognition of complications of central venous catheterization

The number and variety of documented complications of percutaneous central venous catheterization is a sobering influence but the continued use of this technique requires no justification.

On each occasion carefully weigh the advantages to the patient of a central venous line against the risks, in your own unit, of its insertion and maintenance Next, choose the safest route of insertion for the particular patient occasion and operation. For example do not go through infected skin and if a subclavian or low internal jugular[4] venepuncture is planned in a patient with a pre-existing pneumothorax and/or underwater chest drain on one side then perform the venepuncture on that side

Use the technique route of insertion and equipment with which you are most confident and familiar but ensure that the catheter is sterile radiopaque and not too stiff The insertion technique should be "no-touch" and when time permits, conducted as a sterile surgical procedure Do not allow difficulties of access to the patient to compromise sterility Rather remove the obstruction or reselect the route of insertion.

Only radiopaque catheters are acceptable Radiographic inspection of the course and tip of the catheter is essential as soon as possible after its insertion The injection of radiopaque dye down a radio translucent catheter is not an acceptable alternative and may introduce problems of its own such as hypersensitivity reactions, and masking of intrathoracic features on x ray in the case of extravasation of the catheter tip. The advantage of being able to see the catheter on each subsequent chest film is worthwhile Remember that in some patients there may be more than one line (e.g., venous pressure catheter "Swan Ganz" catheter and endocardial pacemaker lead) passing through the same central vein at the same time so knotting may occur

Unfortunately it is often impossible to take a chest film of any kind on a patient as soon as a central venous catheter has been inserted, and prior to its use for fluid infusion. In fact immediate colloid infusion may be life-saving on occasions by the only intravenous route obtainable Consequently any technique of insertion must incorporate immediate bedside checking methods which reduce the possiblity of complications and permit their early recognition should they occur For it is important to realize that major complications can happen any time from within the first minutes to many days following insertion, and this despite the catheter course and tip appearing correctly and safely placed on radiography

To this end the following technical points are suggested

1 Advancement of a correctly located catheter is gentle and easy Resist the temptation to use force

2. Do not coil up a long catheter (e.g., drum cartridge catheter) in the right atrium (or right ventricle[1]) by advancing it too far or too zealously Check the length of your catheter prior to insertion and correlate the length inserted with the patient's dimensions. After all location of the tip in the ipsilateral innominate vein may be perfectly adequate

3. After insertion, and before fixing the catheter—taking the normal precautions to avoid air embolism—attach a syringe containing isotonic saline inject a millimeter or so to clear

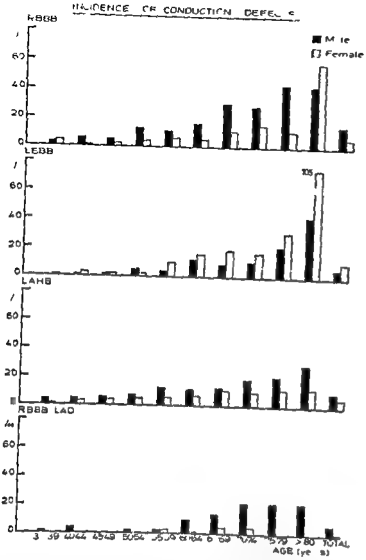

Fig 1 Incidence of complete right bundle branch block (RBBB) left bundle branch block (LBBB) left anterior hemiblock (LAHB) and left axis deviation with RBBB (RBBB-LAD) among 20 000 individuals aged 3o or over attending the mobile screening units of the Province of Liège (Belgium) All figures are expressed in tenths of a per cent except for LAHB where they appear in per cent

Admittedly the present series can in no way be considered unselected but its data stress that even in the presence of overt cardiovascular disease LAD-RBBB is not necessarily an ominous sign and that after all progression towards complete A V block is rather rare The same features have been noted by De Pasquale and Bruno and by Laresse and associates

In 1973 we had set our hopes in His bundle electrocardiography and atrial pacing to identify those patients at greater risk of subsequent appearance of A V block The preliminary results of our experience concur with Puech s view that in LAD-RBBB prolongation of H V interval does not appear to constitute in the short to medium term a supplementary factor indicating the risk of syncope high degree A V block or sudden death This opinion also shared by Denes and colleagues is not fully accepted by Scheinman and co workers who believe that an H V interval greater than 75 msec is undoubtedly of bad prognosis

Another question of importance is the mortality rate in LAD-RBBB Previous prospective studies indicate a high death rate among those patients In series which were much larger than the present one the cumulative two mortality rate was reported at 10 per cent or even 2l cent Severe decrease of survival was also mentioned by Pasquale and Bruno and by McAnulty and associates results which report only one single non cardiac death o two year period significantly differ from those prev studies and deserve some comments

They were obtained from ambulatory examination individuals with or without cardiac symptoms who for most part were still leading a normal or fairly normal lif prospective study based on such a population is likely to y results different from those of investigations carried out subjects selected in the in or out patient s facilities c hospital Preselection of the patients is of course an elemen cardinal importance and one should be careful to av repeating here the mistake which was made a few years ag the discussion of the prognosis of complete left bundle bra block

The benign clinical course of our cases allows so optimism regarding patients with LAD-RBBB Prophylac pacing is surely not recommended although regular medi examinations seem advisable We would like to str however that all prospective studies reported so far (this c included) were concerned with rather short follow up perio Continued studies are needed to define further the long te prognosis of these patients and to determine the factors wh may influence it

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REFERENCES

1 Lenegre J Contribution a l étude des blocs de branch Paris 1958 J B Bailliere et fils
2 Davies M J Pathology of conducting tissue of th heart London 1971 Butterworth and Co
3 Lev M and Unger R M Pathology of the conductio system in acquired heart disease 1 Severe atrioventric ular block Arch Pathol 60 502 1955
4 Sugiura M Okada R Hiraoka K and Ohkawa S Pathohistological studies on conduction system in 1 cases of right bundle branch block with left axis devia tion Jap Heart J 10 121 1969
5 Demoulin J C and Kulbertus H E Histopathologica examination of concept of left hemiblock Br Heart J 34 807 1972
6 Rosenbaum M B Elizari M V and Lazzari J O Los Hemibloqueos Buenos Aires 1968 Los Paidos
7 Lasser R P Haft J L and Friedberg C K Relation ship of right bundle branch block and marked left axis deviation (with left parietal or peri infarction block) to complete heart block and syncope Circulation 37 429 1968
8 Watt T B and Pruitt R D Character cause and consequence of combined left axis deviation and right bundle branch block in human electrocardiograms AM HEART J 77 460 1969

an emergency situation, unintentional removal may have serious consequences.

The great advantage of subclavian or internal jugular venepuncture is that these veins remain patent under all clinical conditions, even in moribund patients of all ages. Despite claims for superiority of one established technique over the other in the past, the important factor is now known to be the care experience or degree of supervision of the operator. Clinicians with responsibilities in any type of acute medicine have an obligation to learn and to maintain their proficiency with a technique for gaining rapid entry to a central vein, in any collapsed adult child or infant patient. ... possessing this expertise equally have an obligation to teach their chosen technique without undue coercion to selected responsible colleagues.

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REFERENCES

1. Davidson, J T Ben Hur N and Nathen H Subclavian venepuncture Lancet 2 1139 1963
2. Yoffa, D Supraclavicular subclavian venepuncture and catheterisation, Lancet 2 614 1965
3. English, I S W Frew R M., Piggott J F and Zaki, M. Percutaneous catheterisation of the internal jugular vein, Anaesthesiology 24 521 1969
4. Deitel, M and MacIntyre J S Radiographic confirmation of the site of central venous pressure catheters, Can J Surg. 14 42, 1971
5. McMahon, M J Hazards of central venous catheterisation Br Med J 3 353 1973
6. Swaroop S Knotting of two central venous monitoring catheters, Am J Med 53 386, 1972.
7. Delfalque R J Fatal complication of subclavian catheter Can Anaes Soc J 18 681 1971
8. Brandt, R.L. Foley W J Fink, C H and Regan W J Mechanism of perforation of the heart with production of hydropericardium by a venous catheter and its prevention Am J Surg 119 311 1970
9. Bone, D K Maddrey W C Eagan J., and Cameron J L. Cardiac tamponade a fatal complication of central venous catheterisation Arch. Surg 106 868 1973
10. Williamson, J Complications of central venous catheterisation Br Med J 4 164 1975
11. Adar R., and Mozes, M Hydromediastinum J.A.M.A 214 372 1970
12. Lumley J and Russell, W J Insertion of central venous catheters through arm veins, Anaes. Intensive Care 3 101 1975
13. Greenall M J Blewitt, R W and McMahon M J Cardiac tamponade and central venous catheters Br Med. J 2 595 1975
14. Delfalque R J Subclavian venepuncture A review Anesth Analg 47 677 1968
15. Arnold, S Feathers, R. S and Gibbs, E Bilateral pneumothoraces and subcutaneous emphysema a complication of internal jugular venepuncture Br Med J 1 211 1973
16. Bansmer G Keith, D and Tesluk, H Complications following use of indwelling catheters of the inferior vena cava J.A.M.A 167 1606 1958
17. Ng, W S., and Rosen M Positioning central venous catheters through the basilic vein, Br J Anaesth 45 1211 1973
18. Dudrick S J., Groff D B., and Wilmore D W Long term venous catheterisation in infants Surg Gynecol. Obstet 129 805 1969

Histochemical evaluation of myocardial preservation by local cooling during anoxia

Preservation of myocardial integrity during open heart surgery is of utmost importance because the outcome of an otherwise successful operation may be disastrous if the myocardium is damaged. When a dry operative field is required and the aorta must be cross clamped selective coronary perfusion or some form of hypothermia has been used to protect the heart from the consequences of anoxia. Coronary perfusion besides being sometimes technically difficult, has a large spectrum of complications, and a number of surgeons have been avoiding it by using varying periods of anoxia with hypothermia. No method however is fully satisfactory and the subject continues to be a widely disputed issue in cardiac surgery. A method introduced by Shumway and Lower involving local cooling of the heart by a continuous flow of chilled saline through the pericardial sac is attractive for both its simplicity and the advantages of avoiding total body hypothermia, and it has been gaining popularity.

The evaluation of these methods has been one of the most difficult problems since control trials are obviously out of the question and the uncontrolled clinical comparisons are very hazardous because of the important influence on the outcome of the operation of so many other variables. Animal experiments have shed light on the mechanisms of myocardial damage during open heart surgery but the results are not directly applicable to the clinical situation.

We reasoned that if we were to study the preservation of the anoxic myocardium during local cooling, we should look for possible changes in cellular function occurring between the beginning and the end of the procedure. Extensive studies done by Niles and co-workers have established that histochemical techniques can be used as sensitive indices of altera

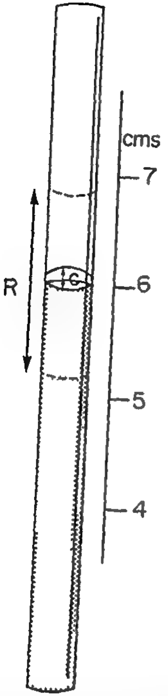

Fig 1 The liquid meniscus in the C V P manometer tubing shows two patterns of oscillation when the catheter tip is adequately positioned in a large central vein a larger amplitude lower frequency oscillation (*R*) produced by ventilation and a smaller amplitude, higher frequency oscillation (*C*) produced by cardiac ventricular action

any clot and aspirate blood gently into the syringe Do not be tempted to use force when aspirating the prospect of biopsying a piece of vein wall is not appealing! If free flowing blood does not come back easily and immediately inject a little more saline withdrawing the catheter 2 cm as you do so Repeat the aspiration test Failure to obtain blood on aspiration is a contraindication to further use of this catheter

4 Fix the catheter to the skin and connect the intravenous fluid line observing that it flows freely Then connect the previously charged manometer limb to the catheter lumen with the three way tap watching the meniscus This should fall immediately and rapidly to a sensible level An errat pressure measurement may be an early sign of an incorrectl positioned catheter

5 Continue close observation of the meniscus and look fo two distinct oscillatory patterns (Fig 1) (a) a larger ampl tude respiratory oscillation and (b) a smaller amplitu higher frequency cardiac oscillation If these are not bot easily visible do not infuse fluid or take pressure readin until the aspiration test is successfully repeated and possible at the time a chest film is taken

6 Whether or not these oscillatory patterns are visible an particularly if they appear damped compress each side of th neck separately with your finger (avoid compressing th carotid sinus!) A rise in the manometer meniscus of mor than 10 cm suggests the catheter tip is located well into th corresponding internal jugular vein Correction for you needs may be possible with radiographic assistance by appro priate withdrawal of the catheter

7 Although a correctly fuctioning transducer will faith fully reproduce these oscillatory patterns the above sequenc should be completed prior to connection to the transduce when circumstances permit

It has been suggested that because of movement of th catheter tip produced by shoulder movement of an arm through which the catheter has been inserted and in consid eration of the level of pericardial reflections around th superior vena cava the tip should not be more than 2 cm below a horizontal line joining the lower surfaces of the media end of each clavicle and the arm should not be abducte beyond 90 degrees Unfortunately these limitations ar impractical in the management of some intensive and coro nary care operating theater and infant patients

Cannulation of the subclavian internal jugular or less commonly femoral veins avoids the several problems asso ciated with arm lines and shoulder movement and despite th risks and reasoned arguments for the use of arm veins other veins will continue to serve a valuable purpose in experienced and careful hands

The maintenance of sterility at the skin puncture site of an central venous line is of the greatest importance but eve with meticulous care infection appears inevitable wit sufficiently long term use The line should always be consid ered a potential source of septicemia It would seem sensible t impose an upper limit on the time for continuous use of th same catheter This limit will be dictated by the diseas patterns staffing and attention to detail possible in indi vidual units but in the writer s experience should be set at 1 days On removal the catheter tip should be sent for bacteri ological culture

Emergency percutaneous cannulation of a central vein in a collapsed neonate or infant patient is a technical problem deserving of closer clinical study but it would appear that the internal jugular vein is a favorable approach However subclavian venepuncture is possible and three successful cases are known to the writer

In order to discourage possible attachment to or perfora tion of the vein wall by a stationary catheter tip it is the writer s practice to withdraw the catheter 1 to 2 cm at the skin on each occasion a dressing is repeated This is followed by a repeat aspiration test for blood It is necessary to know approximately what length of catheter remains inside a central vein before withdrawal is attempted Particularly in

...ut without the serious adverse effects of total body hypo...
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...FERENCES

1. Robicsek F Tam W Daugherty H K and Mullen D C. Myocardial protection during open heart surgery Coronary perfusion versus topical cardiac hypothermia Ann. Thorac. Surg 10 340 19 0
2. Malrnes J V Cooper N Mulder D G and Buckberg G D Depressed cardiac performance after mitral valve replacement A problem of myocardial preservation during operation Circulation 51(Suppl 1) 1 19 4
3. Shumway N E and Lower R R Topical cardiac hypothermia for extended periods of anoxic arrest Surg Forum 10 563 1959
4. Burdette W J and Ashford T P Response of myocardial fine structure to cardiac arrest and hypothermia Ann Surg 158 513 1963.
5. Niles N R Bitensky L Braimbridge M V, and Chayen J Histochemical changes related to oxidation and phosphorylation in human heart muscle J R Microscop Soc 86 159 1966
6. Braimbridge M V Darracott S A R Bitensky L and Chayen J Cytochemical analysis of left ventricular biopsies in open heart surgery A pilot study Beitr Pathol. 148 255 19 3
7. Braimbridge M V Darracott S Clement, A J Bitensky L and Chayen J Myocardial deterioration during aortic valve replacement assessed by cellular biological tests, J Thorac Cardiovasc Surg 66 241 1973
8. Hurley E J Lower R R Dong, E Jr Pillsbury R C and Shumway N E Clinical experience with local hypothermia in elective cardiac arrest J Thorac Cardiovasc Surg 47 50 1964
9. Chayen J Bitensky L. Butcher R., and Poulter L A guide to practical histochemistry Edinburgh 1969 Oliver & Boyd Ltd
10. Chayen J Altmann E P Bitensky L. Braimbridge M V Kadas T and Wells P J A study of the changes in hydrogen transport in an isolated rat heart preparation J R Microscop Soc 86 151 1966

...ow the treadmill[1]

When a diagnostic procedure necessitates the signing of a consent form by the patient the immediate presence of an experienced physician, a defibrillator and necessary drugs for care of cardiac arrest or other serious consequences it must be a dangerous diagnostic procedure Such is the case with the treadmill stress test. One then must ask, Is such a procedure necessary? Is it ever needed? If so when? And What are the criteria for its indication? Also If a serious accident or death were to occur as a result of the procedure could the information that might be acquired justify subjecting the patient to such a risk even a fatal outcome?

With the treadmill, patients are tested quantitatively for cardiac function and potential function under physical stress to evaluate the state and capabilities of their coronary arteries for conducting blood flow But is it quantitative? Can a treadmill program be outlined which could be applied adequately to an 80-year old lady who spends her life in a ... at home and also to a 35-year old jogger who runs 3 to 5 ... per day? Or is a meticulously obtained history of such ... responses to daily activity safer more informative ... clinically more valuable in assessing coronary artery function? If a patient prior to treatment says he cannot walk ... city blocks without chest pain is his coronary arterial ... known less or better than if he is tested on the treadmill? Is a treadmill test more accurate quantitatively than a meticulous history of the patient s responses to daily ... activity and psychic stress? After all, people live in ... gardens, streets, offices etc., and not on a moving ... surrounded by flashing lights, defibrillators complicated apparatus disgorging scrolls of paper syringes, drugs busy grim nurses and doctors in white Furthermore the hazardous treadmill test costs $100 00 or more whereas the history of performance is routinely obtained by any well trained conscientious cardiologist anyway Not many years ago even cardiologists were reluctant to subject their patients to Master s 2 step test a much milder and more appropriate test Were they right or wrong then? Did they miss something in the clinical cardiac study?

With all of the new expensive and hazardous diagnostic and therapeutic procedures of today is the life span of man being extended? Or even the life span of one man? The H E W Life Tables show slight to no increase in the life span of Americans for the past 20 years. When the books are balanced" with proper consideration of information derived from the treadmill test versus the expense risk, damage and even possible death associated with the test is man better off" with the treadmill or not? These questions must be answered But who is to answer them? Who will outline criteria for application of the test, be responsible for serious reactions and control costs? The patient is usually impressed with the procedure but he is in no position to understand or know the indication value or risks involved Initially the treadmill was used only in the hospital where adequate facilities were available to manage properly any adverse responses to the exercise test including cardiac arrest Now the treadmill is being employed in the physician s office

So now the treadmill! What next? Can anything be admitted into the practice of medicine and be accepted

[1] ...erican

Table I Grading of histochemical changes

Case No	Procedure	Time of bypass (min.)	Time of aortic cross clamping (min.)	Total score at start of bypass	Total score at end of bypass	Total score change
1	AVR*	120	90	6.5	5	−1.5
2	AVR	97	72	7	6.5	−0.5
3	AVR	112	65	5	7.5	+1.5
4	AVR	117	70	5.5	7.5	+0.5
5	AVR	168	103	7.5	[illegible]	+0.5
[illegible]	AVR	101	80	5	8	+0.5
7	AVR	[illegible]	63	7.5	4	−1
8	MVP*	52	7	9	5.5	−2
9	MVP	80	47	3.5	9	0
10	MVP	110	33	4	4	+0.5
11	MVP	95	34	8	4.5	+0.5
12	MVP	107	60	3.5	7.5	−0.5
13	MVP	145	12	6.5	5	+1.5
14	MVP	75	36	7	6.5	0
15	MVR*	100	54	7.5	6.5	−0.5
16	MVR	105	30	9	7	−0.5
17	MVR	100	12	5.5	8	−1
18	MVR	74	20	6.5	6.5	+1
19	MVR	45	13	9	6.5	0
					7	−1.5

AVR = Aortic valve replacement MVR = mitral valve replacement MVP = mitral valvuloplasty

tions in myocardial function These have been successfully used at St Thomas's Hospital London to predict postoperative function of the myocardium[6,7]

The integrity of the cytoplasmic structure energy production via oxidative mechanisms and energy utilization for contraction of the myocardial cell can be assessed by the histochemical reactions of acid hematin monoamine oxidase cytochrome oxidase succinodehydrogenase and adenosine triphosphatase (ATPase)

In 19 cases of aortic and mitral valve surgery done in Athens utilizing anoxia and local pericardial cooling for the whole period of the bypass samples of the left ventricular wall were obtained by drill biopsy at the beginning and end of the bypass These were immediately chilled to −70 C and sent to London where the above histochemical tests were performed on frozen sections as described elsewhere The result was assessed by a single observer blind to the origin of the sample and was expressed in a semiquantitative way grading the changes as follows 0 = normal 1 = fairly normal 1 to 3 = moderate 2 = poor and 3 = bad The total score of each biopsy was a measure of the degree of myocardial cell damage In Table I the total score is shown of the biopsies taken at the beginning and end of the operation In the majority of cases the score either improved at the end of the operation or deteriorated slightly In three cases however increases of 1½ in two cases and 3 in one case were noted probably indicating a slight degree of myocardial damage Changes in total score of similar magnitude in the direction of improvement however challenge the validity of this statement or these latter changes themselves require interpretation

Acid hematin reaction detects free phospholipids within the cytoplasm which are probably liberated from the lipid protein complexes of membranous structures presumably following an insult The monoamine oxidase and cytochrome oxidase reactions relate to the integrity of the mitochondrial oxidative mechanisms which decrease under hypoxic conditions whereas the succinodehydrogenase an important enzyme of the Krebs cycle is normally found uniformally distributed along the myofibrils This has been thought to be related to a hydrogen transporting system from mitochondria to myofibrils Finally the ATPase activity in the cell is due to myocin itself thus allowing detection of changes in the contractile system

Although these histochemical tests do assess a variety of aspects of cell functions other important adverse changes may remain undetected Neither does the detection of changes in the two different biopsies guarantee that they cannot be due to the sampling site or to an unforeseen difference in the technique

It is of interest however that although there was a wide difference in the total score among the biopsies of the different patients taken at the beginning of the operation there were much smaller differences seen between the beginning and the end We concluded therefore that these results indicate good myocardial preservation by local cooling during bypass In addition quite serious changes may be present at the beginning of the bypass due either to cardiac failure or possibly to the anesthesia and the operation up to that stage Finally in some cases slight deterioration and in some others slight improvement in myocardial function occurred during anoxia with local cooling The last might presumably be due to the recovery of cellular integrity associated with the slowing down of biochemical activity during cooling

Apart from the obvious importance of these observations for the evaluation of local cooling during bypass they raise the interesting possibility of a role of cooling in decreasing infarct size following a coronary attack Unfortunately there is no obvious way in clinical myocardial infarction of cooling the

heart without the serious adverse effects of total body hypothermia.

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REFERENCES

1. Robicsek, F Tam, W Daugherty H K and Mullen D C Myocardial protection during open heart surgery Coronary perfusion versus topical cardiac hypothermia. Ann Thorac. Surg 10 340 1970
2. Maloney J V Cooper N Mulder D G and Buckberg G D Depressed cardiac performance after mitral valve replacement A problem of myocardial preservation during operation Circulation 51(Suppl 1) 1 1974
3. Shumway N E., and Lower R R Topical cardiac hypothermia for extended periods of anoxic arrest Surg Forum 10 563 1959
4. Burdette W J and Ashford T P Response of myocardial fine structure to cardiac arrest and hypothermia Ann Surg 158 513 1963
5. Niles N R., Bitensky L. Braimbridge M V and Chayen J Histochemical changes related to oxidation and phosphorylation in human heart muscle J R Microscop Soc 86 159 1966
6. Braimbridge M V Darracott S A R Bitensky L and Chayen J Cytochemical analysis of left ventricular biopsies in open heart surgery A pilot study Beitr Pathol 148 255 1973
7. Braimbridge M V Darracott S Clement A J Bitensky L and Chayen J Myocardial deterioration during aortic valve replacement assessed by cellular biological tests J Thorac Cardiovasc Surg 66 241 1973
8. Hurley E J Lower R R Dong, E Jr Pillsbury R C and Shumway N E Clinical experience with local hypothermia in elective cardiac arrest J Thorac Cardiovasc Surg 47 50 1964
9. Chayen J Bitensky L. Butcher R and Poulter L A guide to practical histochemistry Edinburgh 1969 Oliver & Boyd Ltd
10. Chayen J Altmann F P Bitensky L Braimbridge M V Kadas, T and Wells, P J A study of the changes in hydrogen transport in an isolated rat heart preparation J R Microscop Soc 86 151 1966

Now the treadmill!

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So now the treadmill! What next? Can anything be admitted into the practice of medicine and be accepted

without prior careful evaluation? There is a need for objective evaluation of such diagnostic procedures before they are introduced into general clinical use just as now exists for drugs

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REFERENCE

1 Vital Statistics of the United States Life Tables, U.S Department of Health Education and Welfare Publi Health Service Washington D C 1973 Vol II Sectio 5

Letters to the Editor

Complication of right ventricular myxoma

To the Editor

I enjoyed reading the article "Diagnostic features of right ventricular myxoma" by Snyder and associates in the February 1976 issue of the AMERICAN HEART JOURNAL (91 240 1976). One notes that no gradient was present across the tricuspid valve in their patient. We reported a case of right ventricular myxoma causing obstruction across both the tricuspid and pulmonary valve in the July 1973 issue of the *American Journal of Cardiology*.

The bibliography in the Snyder article reviewed the literature up to the year 1971 which failed to emphasize obstruction to right ventricular inflow as well as outflow. Our patient's symptoms of edema extending to the waist accompanied by fatigue and dyspnea had been a tell tale symptom.

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REFERENCE

1. Zager J Smith, J O Goldstein S and Franch R H Tricuspid and pulmonary valve obstruction relieved by removal of a myxoma of the right ventricle Am J Cardiol. 32 101 1973

Reply

To the Editor

I wish to thank Dr Zager for his comments on our article. We are aware of the inflow tract obstruction which may be produced by right ventricular myxoma but since our patient did not have a gradient across the tricuspid valve we did not comment on this complication.

We certainly appreciate Dr Zager's interest and hope that his letter will remind your readers of this potential complication of right ventricular myxomas.

Stanley N Snyder M D
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The phonocardiogram in right ventricular myxoma

To the Editor

Snyder and associates report an interesting case of right ventricular myxoma (AM. HEART J 91 240-248 1976). These authors make an issue of the finding of wide splitting of the second heart sound due to a delayed pulmonic closure. But is that early diastolic sound the pulmonic closure sound? The simultaneous jugular pulse tracing shows that the sound labeled P occurs more than 50 msec after the opening of the tricuspid valve as determined by the peak of the "V" wave. If the authors postulate that the pulmonic valve remains open in early diastole because of the tumor what produces its ultimate closure?

The authors refer to a previous report of a right ventricular tumor that was also associated with an early diastolic sound[1]. The authors of that report were not certain about the origin of the sound nor did they show data to suggest its connection to the pulmonic closure.

Since the early diastolic sound coincides with the rapid filling phase of the right ventricle and there is also a late diastolic sound following atrial systole it is reasonable to assume that they are indeed related to ventricular filling and most likely produced either by the tumor hitting the ventricular wall or by abnormal intraventricular flow patterns induced by the tumor. The prominent "a" wave on the phlebogram suggests the latter.

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REFERENCE

1. Sakakibara S Osawa M Konno S et al Myxoma of the right ventricle of the heart Report of a case with successful removal and review of the literature AM. HEART J 69 382 1965

Reply

To the Editor

Dr Levisman's comment on the etiology of the prominent early diastolic sound are appropriate. We felt that the sound represented a combination of events of which closure of the pulmonic valve could not be excluded. Certainly the protrusion of the tumor mass through the pulmonic valve contributed to the events during late systole and early diastole. Whether it was the tumor mass the closure of the pulmonic valve or the presence of pulmonary emboli, or some combination thereof that caused this sound is difficult to ascertain and we recognize the difference of opinion. It was conceivable to us that a ball valve like effect of the tumor protruding into the pulmonary artery could maintain the pulmonic valve in the open position during right ventricular filling. Then as the right ventricular cavity enlarged, the tumor mass as the separation between the free right ventricular wall and intraventricular septum increased could retreat from its position in the pulmonary artery and return to within the right ventricular cavity. If this process occurred abruptly during right ventricular dilatation the valve with sudden relief of pressure could conceivably suddenly snap shut producing a delayed and accentuated P.

We also felt that atrial systole certainly could disturb the tranquility of the tumor mass in the right ventricle and set up a vibration but we concluded since there was such a prominent A wave in the jugular venous pulse that the S was produced by the same mechanism as the S in other disease

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1. Sakakibara, S., Osawa, M., Konno, S., et al.: Myxoma of the right ventricle of the heart. Report of a case with successful removal and review of the literature, AM. HEART J. 69:382, 1965.

Reply

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We also felt that atrial systole certainly could disturb the tranquility of the tumor mass in the right ventricle and set up a vibration but we concluded, since there was such a prominent A wave in the jugular venous pulse, that the S_4 was produced by the same mechanism as the S_4 in other disease

states where the right atrium attempts to augment right ventricular filling. In this case the prominent A wave and the S may be due to right ventricular overload secondary to decreased right ventricular compliance which may occur following pulmonary embolism or obstruction to right ventricular outflow due to the tumor. Contrariwise, if the S did not follow a prominent A wave in the jugular venous pulse, then we would be at a loss to explain its etiology and would have to assume it was due to disturbance of the tumor position by normal atrial systole.

We agree with Dr. Levisman's observation that Sakakibara and associates (his Reference 1) did not present data to suggest a specific relationship of the early diastolic sound to pulmonic closure, but we were influenced by their statement that although the abnormal vibratory phenomena was recorded over the entire precordial area, it did have its maximal intensity at the pulmonary focus, as was also present in our case. Because of the location of the maximum intensity of the sound we could not dispel a possible relationship between it and pulmonic valve closure. I hope that the above comments will answer some of Dr. Levisman's questions.

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Transchest electrical ventricular defibrillation

To the Editor:

The statement that "defibrillators presently available cannot deliver a dose that is adequate to defibrillate consistently the ventricles of most patients who weigh 60 kilograms or more" is based primarily on data derived from animal experimentation, and on a single retrospective study in patients. The interpretation of the human study is open to question since the reason for a lower success rate in subjects weighing more than 50 kilograms might well be the higher incidence of significant pre-existing cardiovascular disease in adults. Furthermore, the number of very heavy patients (more than 90 kilograms) was quite small.

A prospective study was published more recently by the Belfast group with a comparable number of patients weighing more than 50 kilograms and in particular a larger number of patients in the crucial group weighing more than 90 kilograms. They used a very low delivered energy of 150 to 165 watt-seconds with a very respectable rate of success. The clinical data indicating the need for high energy defibrillation are at best controversial. The data indicating that low energies are adequate is much more compatible with our experience at UCLA. In 1975, in our capacity as a Paramedic Base Station we participated in the care of 302 patients who experienced sudden cardiac arrest outside the hospital. The paramedic squads are equipped with commercially available defibrillators producing a Lown wave form and uniformly employ the 400 watt-second energy setting for defibrillation. The delivered energy is probably in the 250 to 320 watt-second range. It is our distinct impression that our rate of successful defibrillation is high, even in heavy patients.

Therefore, it would seem premature to recommend the manufacture and sale of defibrillators with very large energy output since such a trend would lead to heavier, more expensive, less portable defibrillators and to increased potential for myocardial damage due to the delivery of excessive electrical doses to some patients.[5] Additional clinical studies should be undertaken to verify the need for higher energy outputs in human ventricular defibrillation.

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REFERENCES

1. Ewy, G. A., and Tacker, W. A.: Transchest electrical ventricular defibrillation, AM HEART J 91:403, 1976.
2. Geddes, L. A., Tacker, W. A., Rosborough, J. P., et al.: Electrical dose for ventricular defibrillation of large and small animals using precordial electrodes, J Clin Invest 53:310, 1974.
3. Tacker, W. A., Galioto, F., Guiliani, E., et al.: Energy dosage for human transchest electrical ventricular defibrillation, N Engl J Med 290:214, 1974.
4. Pantridge, J. F., Adgey, A. A. J., Webb, S. W., et al.: Electrical requirements for ventricular defibrillation, Br Med J 2:313, 1975.
5. Dahl, C. F., Ewy, G. A., and Warner, E. D.: Myocardial necrosis from direct current countershock, Circulation 50:956, 1974.

Reply

To the Editor:

We appreciate the response from Drs. Morgan and McElroy and fully agree that additional clinical studies should be undertaken to verify the need for higher energy output for human ventricular defibrillation. A group such as theirs might be ideal to gather these data by noting defibrillatory energy settings, weight of the patient, and the success and/or failure of the first few defibrillatory countershocks. Since the transthoracic impedance to direct current countershock decreases with successive defibrillatory discharges, a unit that delivers borderline energy might be successful after a few or several countershocks. The goal should be to deliver adequate energy for defibrillation with the first countershock.

The prospective study by the Belfast group has been expanded in their book *The acute coronary attack*. Their latest data indicate that of 144 episodes of ventricular fibrillation, 124 (86 per cent) were converted to another rhythm by a single low energy countershock, whereas in 11 a second and in 2 a third countershock was necessary. Their results can be summarized as follows:

Patient wt Kg	Success rate (%)
< 60	100
< 80	[illegible]
> 80	85
>100	70

This experience suggests that the energy level needed for human ventricular defibrillation might well be lower than that for ventricular defibrillation of animals. However, the

trend of decreasing success rate of human ventricular defibrillation with increasing body weight is again confirmed. This observation cannot be ignored. In both the study by Tacker and associates and the study by Pantridge and associates, there were heavy subjects who were defibrillated. However careful analysis of the data was required to demonstrate the difficulty of defibrillating heavy patients.

If and when higher energy defibrillators become available it will no longer be acceptable to discharge the units at maximal settings irrespective of patient size. The "dose concept" for ventricular defibrillation will need to be used to avoid myocardial damage.

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REFERENCES

1. Geddes, L. A., Tacker, W. A., Cabler, P., et al: The decrease in transthoracic impedance during successive ventricular defibrillation trials, Med. Instrument 9: 1 9, 19 5
2. Pantridge, J. F., Adgey, A. A. J., Webb, S. W., et al: Electrical requirements for ventricular defibrillation, Br. Med. J. 2: 313, 19 5
3. Pantridge, J. F., Adgey, A. A. J., Geddes, J. S., et al: The acute coronary attack, New York, 19 5, Grune & Stratton, Inc., p. 66- 8.
4. Tacker, W. A., Galioto, F., Giuliani, E., et al: Energy dosage for human trans-chest electrical defibrillation, N. Engl. J. Med. 290: 14, 19 4

Method of reporting and evaluating the results of treadmill exercise testing

To the Editor:

Although treadmill exercise testing is a widely used screening procedure for the detection of coronary ischemia and is recognized to contain hemodynamic information, no codified system for meaningful reporting of its results exists.

We therefore propose the following formula which accounts for both heart rate (HR) and mean arterial blood pressure (MABP) changes in exercise—called "exercise index" (EI):

$$\mathrm{EI} = \frac{\text{(exercise change of HR} \times 100)}{\text{basal HR}} \times \frac{\text{(exercise change of MABP} \times 100)}{\text{basal MABP}}$$

$$\text{and where MABP} = \frac{\text{systolic} + 2 \times \text{(diastolic)}}{3}$$

This EI has been validated in a series of 164 men (?7 to ?4 years old) subjected to a well known exercise protocol. The end point of exercise was either physical exhaustion or production of angina. The criterion of electrocardiographic (ECG) positivity was ST segment depression ≥ 1 mm lasting up to 0.08 sec. after the J point. The exercise parameters were gathered within the first 30 sec. after the end of the treadmill test. The mean values and the standard errors of the means (SEM) for the EI as correlated to the history and the ECG outcome are given in Table I.

The proposed EI discriminates significantly among mean values, between positive and negative ECG outcomes ($p < 0.001$) and also detects differences between angina negative cases ("false negatives") and both angina positive ($p < 0.05$) and atypical negative cases ($p = 0.05$), making it possible to advance the hypothesis that "false negatives" may express coronary cases with relatively conserved myocardial oxygen supply reserves and leading to the inference that they might represent less anatomically advanced coronary artery disease. It is apparent from the above that the proposed EI performs quantitatively well.

The combination of this index with the duration of exercise for each of the cases studied coupled to the classification angina positive contrasted with atypical negative cases is shown in Table II.

Only 3.44 per cent (1/29) of the angina cases with positive ECG outcome had both parameters simultaneously in the upper quartiles, whereas only 3.15 per cent (3/95) of those with atypical chest complaints and negative ECG outcome had both parameters simultaneously in the lower quartiles. This is indeed a very remarkable practical performance. Besides, the lower quartiles of EI and/or of duration of exercise comprised 72.4 per cent (21/29) of the angina positive cases vs. 27.3 per cent (?6/95) of atypical negative cases ($p < 0.01$). Also the upper quartiles of each or both of the above parameters comprised 13.8 per cent (4/?9) of angina positive vs. 60 per cent (57/95) of atypical negative cases ($p < 0.01$).

From these facts it is evident that the combination of the EI and the duration of exercise constitutes a meaningful and valuable method for classifying and reporting exercise test

Table I. EI correlated with history and ECG outcome

History	ECG outcome	No	EI Mean	EI SEM	Significance of differences		
1. Angina	Pos.	29	793.8	131.0	1 vs. 2	t = 1.64	p > 0.1
2. Atypical	Pos.	10	1442.1	3 30	1 vs. 3	t = 2.11	p < 0.05
3. Angina	Neg.	30	1273.4	185.0	2 vs. 4	t = 0.71	p > 0.4
4. Atypical	Neg.	95	1 24.6	134.0	3 vs. 4	t = 1.98	p = 0.05
5.	All pos.	39	960.0	141.0			
[illegible]	All neg.	1[illegible]5	1616.3	112.0	5 vs. 6	t = 3.63	p < 0.001

states where the right atrium attempts to augment right ventricular filling In this case the prominent A wave and the S may be due to right ventricular overload secondary to decreased right ventricular compliance which may occur following pulmonary embolism or obstruction to right ventricular outflow due to the tumor Contrariwise if the S did not follow a prominent A wave in the jugular venous pulse then we would be at a loss to explain its etiology and would have to assume it was due to disturbance of the tumor position by normal atrial systole

We agree with Dr Levisman s observation that Sakakibara and associates (his Reference 1) did not present data to suggest a specific relationship of the early diastolic sound to pulmonic closure but we were influenced by their statement that although the abnormal vibratory phenomena was recorded over the entire precordial area it did have it maximal intensity at the pulmonary focus as was also present in our case Because of the location of the maximum intensity of the sound we could not dispel a possible relationship between it and pulmonic valve closure I hope that the above comments will answer some of Dr Levisman s questions

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Transchest electrical ventricular defibrillation

To the Editor

The statement that defibrillators presently available cannot deliver a dose that is adequate to defibrillate consistently the ventricles of most patients who weigh 80 kilograms or more is based primarily on data derived from animal experimentation and on a single retrospective study in patients The interpretation of the human study is open to question since the reason for a lower success rate in subjects weighing more than 50 kilograms might well be the higher incidence of significant pre existing cardiovascular disease in adults Furthermore the number of very heavy patients (more than 90 kilograms) was quite small

A prospective study was published more recently by the Belfast group with a comparable number of patients weighing more than 50 kilograms and in particular a larger number of patients in the crucial group weighing more than 90 kilograms They used a very low delivered energy of 150 to 165 watt seconds with a very respectable rate of success The clinical data indicating the need for high energy defibrillation are at best controversial The data indicating that low energies are adequate is much more compatible with our experience at UCLA In 1975 in our capacity as a Paramedic Base Station we participated in the care of 302 patients who experienced sudden cardiac arrest outside the hospital The paramedic squads are equipped with commercially available defibrillators producing a Lown wave form and uniformly employ the 400 watt second energy setting for defibrillation The delivered energy is probably in the 250 to 320 watt second range It is our distinct impression that our rate of successful defibrillation is high even in heavy patients

Therefore it would seem premature to recommend the manufacture and sale of defibrillators with very large energy output since such a trend would lead to heavier more expensive less portable defibrillators and to increased potential for myocardial damage due to the delivery of excessive electrical doses to some patients [5] Additional clinical studies should be undertaken to verify the need for higher energy outputs in human ventricular defibrillation

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REFERENCES

1 Ewy G A and Tacker W A Transchest electrical ventricular defibrillation AM HEART J 91 403 1976
2 Geddes L A Tacker W A Rosborough J P et al Electrical dose for ventricular defibrillation of large and small animals using precordial electrodes J Clin Invest 53 310 1974
3 Tacker W A Galioto F Guiliani E et al Energy dosage for human transchest electrical ventricular defibrillation N Engl J Med 290 214 1974
4 Pantridge J F Adgey A A J Webb S W et al Electrical requirements for ventricular defibrillation Br Med J 2 313 1975
5 Dahl C F Ewy G A and Warner E D Myocardial necrosis from direct current countershock Circulation 50 956 1974

Reply

To the Editor

We appreciate the response from Drs Morgan and McElroy and fully agree that additional clinical studies should be undertaken to verify the need for higher energy output for human ventricular defibrillation A group such as theirs might be ideal to gather these data by noting defibrillatory energy settings weight of the patient and the success and or failure of the first few defibrillatory countershocks. Since the transthoracic impedance to direct current countershock decreases with successive defibrillatory discharges a unit that delivers borderline energy might be successful after a few or several countershocks The goal should be to deliver adequate energy for defibrillation with the first countershock

The prospective study by the Belfast group has been expanded in their book *The acute coronary attack* Their latest data indicate that of 144 episodes of ventricular fibrillation 124 (86 per cent) were converted to another rhythm by a single low energy countershock whereas in 11 a second and in 9 a third countershock was necessary Their results can be summarized as follows

Patient wt Kg	Success rate (%)
< 60	100
< 80	98
> 80	85
>100	70

This experience suggests that the energy level needed for human ventricular defibrillation might well be lower than that for ventricular defibrillation of animals However the

Symposium uber Probleme der Kard o-vaskularen Regulation. Edited by Prof Dr med. R Baumann and Prof Dr med I. E Schchwazabaja, Berlin 19 5 Akademi Verlag 634 pages.

This book written in German contains the papers presented at a German Soviet symposium held in 1973 on hypertension and biochemical mechanisms of cardiovascular regulations. The importance of these two aspects of cardiovascular diseases is well known. This symposium reviewed some of the concepts among German and Russian investigators. The emphasis is on hemodynamic studies, but clinical investigations and management are discussed. The series of many short papers should interest physiologists primarily. The contributors really summarize their respective investigations in about papers of about 2 to 6 pages each. This review is presented in the usual fashion for proceedings of symposia. This publication contains a great deal of information concerning important problems in cardiovascular diseases.

Cardiovascular dynamics. 4th edition. By Robert F Rushmer M D Philadelphia 19 6, W B Saunders Company 584 pages.

This fourth edition of *Cardiovascular Dynamics* attests to the reception and usefulness of Rushmer's book. It is a good presentation of difficult pathophysiologic and normal functional aspects of the cardiovascular system. Many of the generally accepted concepts are debatable and provocative. However the presentations are clear and nicely illustrated. This book should interest students, house staff, and busy practicing doctors, whereas physiologists and investigators will find a more extensive knowledge of the literature than presented in the brief references necessary to understand better the problems related to the function of the cardiovascular system in health and in disease. The book is a good condensed presentation of "facts" as presently accepted for the use in clinical practice by doctors and students.

Cardiac Physiology for the Clinician. Edited by Mario Vassalle M D New York 19 6 Academic Press, Inc 63 pages. Price $18.50

This is a very good book for practicing cardiologists who must know normal and abnormal physiology in order to appreciate the symptoms and signs of heart disease. The contributors are outstanding authorities in their respective fields and the subjects discussed are most appropriate even though they may at first glance appear esoteric. The subjects discussed include electrophysiology of the heart, contractility of the myocardium, neural control of the heart, arrhythmias and antiarrhythmal drugs, hypertrophy and therapy. This is a highly recommended book.

Progress in Respiration Research volume 9 Pulmonary Hypertension. Edited by J Widimsky Basel 19 5 S Karger AG 318 pages. Price $72.00

This is an expensive ($ .00) publication of a symposium held in Prague on June 1 to 1 1974 on Pulmonary Hypertension. The subject is a most important and difficult problem in clinical medicine. Pulmonary hypertension due to chronic pulmonary disease, altitude, and congestive heart failure were the three main disturbances discussed at the symposium. The series of papers is interesting and useful to physicians and students. This is a highly recommended book on a most difficult problem in clinical medicine.

Postoperative Congenital Heart Disease. Edited by Amnon Rosenthal, M D Edmund H Sonnenblick M D., and Michael Lesch M D., New York 19 5 Grune & Stratton Inc., 166 pages. Price $14.50

This is a bound reprint of the issue of *Progress in Cardiovascular Diseases on Postoperative Congenital Heart Disease*. Those who already received the publication will not need to buy this book, whereas others who do not will find this to be a nicely bound reprint. The subject is an important one for cardiovascular surgeons and cardiologists. This issue of *Progress in Cardiovascular Diseases* is a good one and of practical clinical importance.

Table II EI correlated with duration of exercise

Duration of exercise quartiles	EI Quartiles							
	Lower		Middle two		Upper		Total	
	Ang P*	At N	Ang P	At N	Ang P	At N	Ang P	At N
Lower								
Ang P	12		4		1		17	
At N		3		7		2		12
Middle two								
Ang P	3		6		0		9	
At N		10		18		11		39
Upper								
Ang P	1		1		1		3	
At N		4		23		17		44
Total	16	17	11	48	2	30	29	95

Ang P = angina positive At N = atypical negative

results It also permits an insight into the meaning of false negative and false positive exercise cases

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REFERENCES

1 Detry J M R Piette F and Brasseur L A Hemodynamic determinants of exercise ST segment depression in coronary patients Circulation **42** 593 1970
2 Doan A E Peterson D R Blackmon J R and Bruce R A Myocardial ischemia after maximal exercise in healthy men AM HEART J **[illegible]** 21 1965
3 MacHenry P L Phillips J F and Knoebel S B Correlation of computer quantitated treadmill exercise electrocardiogram with arteriographic location of coronary artery disease Am J Cardiol **30** 747 1972
4 Cheitlin M D Davia J E DeCastro C M Barrow E A and Anderson W T Correlation of critical left coronary lesions with positive submaximal exercise tests in patients with chest pain AM HEART J **89** 305 1975
5 Sketch M H Mohiuddin S M Lynch J D Zencka A E and Runco V Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms Am J Cardiol **36** 169 1975
6 Tselos S Goldman S and Cohn K Marked depth and duration of ST depression as indicators of extensive coronary disease Am J Cardiol **35** 174 1975

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Books received

Planning a Course of Continuing Education for General Practice—A Systematic Approach By Roger B Cole M D and Charles E Engel London 1976 British Medical Association 42 pages

Children with Congenital Intracardiac Defects Edited by Leona M Bayer M D and Marjorie P Honzik Ph D Springfield Ill 1975 Charles C Thomas Publisher 260 pages Price $35 75

The Lung in the Critically Ill Patient Edited by William C Shoemaker M D Baltimore 1976 The Williams & Wilkins Company 125 pages Price $9 50

Arrhythmia Analysis by Intracardiac Electrocardiography By John W Lister M D Arthur J Gosselin M D Eugene J Sayfie M D and Milton E Lesser M D Springfield Ill 1975 Charles C Thomas Publisher 322 pages Price $34 50

My Autobiography and Medical Advice to Our Disturbed World By Louis H Sigler M D New York 1975 Vantage Press Inc 43 pages Price $4 50

Monographs on Atherosclerosis vol 6 Bile Acids Chemistry and physiology of bile acids and their influence on atherosclerosis By William T Beher Basel New York 1976 S Karger AG 225 pp Price $39 00

Neonatal and Pediatric Cardiopulmonary Care A Self Assessment By Thomas J Williams Chicago 1976 Year Book Medical Publishers Inc 224 pp

The Practice of Medicine A Self Assessment Guide Edited by Simeon Margolis with A McGehee Harvey Richard J Johns Albert H Owens Jr and Richard S Ross New York 1976 Appleton Century Crofts Inc 396 pp Price $11 50

Announcements

Selected Topics in Cardiology

The University of Texas Health Science Center at Houston Division of Continuing Education will sponsor a seminar entitled Selected Topics in Cardiology to be held in Houston Texas on December 7 through 9 1976 Dr H J C Swan Chairman of the Division of Cardiology of the Cedars Sinai Medical Center Los Angeles will join the list of distinguished guest lecturers as the James J and Una Truitt Lecturer for 1976 The program will consist of a review of selected topics in cardiology including valvular heart disease coronary heart disease and cardiac physiology

For further information please write Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education P O Box 20367 Houston Texas 77025

Psychosocial care of the dying patient

The Cancer Research Institute and Extended Programs in Medical Education University of California School of Medicine San Francisco California will present a postgraduate course in Psychosocial Care of the Dying Patient June 3 and 4 1977 Basic issues in psychosocial care will be outlined allowing the physician to acquire a working knowledge of the effective care of the dying patient Focus will center upon the sequence of events generally encountered by the physician and the terminally ill patient from diagnosis through death For additional information please contact Charles A Garfield Ph D Program Chairman University of California San Francisco School of Medicine San Francisco Calif 94194

Editorial

Of venture research

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Medical and biomedical research is excessively tailored today to conform to the conventional great problems in medicine These programs are committee initiated in many instances and these committees react to agendas in research outlined by unknown individuals whose intentions are noble but whose motivations are dependent upon money and public opinion neither of which originates from the public directly or necessarily from a master or dedicated scientist Unfortunately these directives and operations really represent a form of contract research This is not only true in government supported programs but in private ones as well Large sums of money are poured into programs established by individuals or committees and oriented to reflect opinions of groups of individuals The sources of these funds are public in large part including tax exempt foundations Under such principles of operations crash programs under various names are rapidly developed followed by announcements circulated and published Laboratory directors and grant managers institutions and individuals respond to these announcements with various forms of grant applications in order to gather some of these readily available funds Although this practice results in the accumulation of data thoughtful deliberate and highly motivated outstanding high quality research usually does not follow Old things are rediscovered by different people with new tools and methods New discoveries rarely occur Time money and people are wasted Research training and discipline are poor and the quality of research suffers It is better not to do research or not to train research personnel if the quality of research is poor and if the training is in an environment of pseudo investigations Some non-disciplined programs are to be expected and can be tolerated but great discoveries will not be forthcoming Such research is generally more technologic anyway However these programs must not receive support to the exclusion of venture research or research in the search of knowledge for the sake of knowledge

In the milieu of tremendous effort in medical and biomedical research there is a need to support and foster venture research a form of theoretic medical research comparable in nature to theoretic physics and mathematics Venture research is the type of research that will most likely provide the important great discoveries and major advances in knowledge even though it may not be popular or exciting at the time

There is a need for granting agencies to seek out investigators who are genuinely interested in research and exploration of the unknown to advance knowledge for the sake of knowledge These people should receive minimal support and be left alone without the annoyances and distractions imposed by grant applications reviewing committees and pressure to publish Data and curve collecting must not be a source of disturbance I doubt that any unknown general practitioner delivering babies today would receive support to study the heart beat Sir James McKenzie would have had his grant application disapproved based on many obvious present standards of grant award How would Roentgen have written his grant application to discover x ray or Nicolle to discover polarized light or the Curies to discover natural radiation or Fleming to

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So finally let us make sure that the thinkers who are allowed to advance knowledge for the sake of knowledge itself are provided with the security of a livelihood so they can think and work creatively in peace and quiet

May we support with vigor imagination and vision Venture Research for search into the unknown for the sake of knowledge itself

REFERENCES

1. Burch, G E. Of one mind, AM HEART J 89 127 1975
2. Wade N Discovery of pulsars a graduate student's story Science 189 358 19[illegible]
3. Burch G E. Of scientific thought, Arch. Intern. Med 102 [illegible] 1958

discover penicillin or a 19 year old female graduate student to discover x radiation from the galaxies in outer space, and so on? No one can write an application describing planned studies and results to be obtained for a great discovery or a major fundamental advancement in science or knowledge Even the investigator fails to know in advance that he is to make a truly great new advancement in knowledge But what are these great new discoveries worth in money health happiness and well being of people today? We need these discoveries, and so venture research *must* be developed by thinkers who are left alone to their thoughts

Americans should be financially able and wise enough to provide a few people with $35,000 to $40,000 per year to do whatever research they want—alone, free from frustration, to think to delve into the unknown, to satisfy their curiosity Can't we Americans afford to gamble a little on a few real scientists? Who are the peers of Fleming Madam Curie, Roentgen Nicolle Gauss or Newton? These are people without peers What committee could have reviewed Einstein s thoughts in advance of their creation? There is a need to gamble with some funds to aim our research objectives at the highest levels Remember the life expectancy of man in the U S A has not advanced significantly if at all in the last quarter century in spite of center grants SCOR grants crash programs large quantities of funds and much time and effort So let us support individuals for years purely on the basis of the person and creative thinking Give them minimal security and minimal support and leave them alone in peace to think observe and study without having to spend valuable time giving an account of themselves with periodic reports applications lectures and publications An occasional reprint or an occasional friendly scientific helpful but not inspector s visit to them might be acceptable or considered There would be no need or justification for a formal periodic inspection That would ruin everything We need to support thinking and the best minds of Americans Remember, the strength of America resides in the minds of Americans [3]

There is a need for Scientific America' to have absolute confidence in at least a few scientists The cost would be minimal and the results could be tremendous The objective would be to let some of the great minds alone and free to thin[k] Only an occasional person or maybe only one c[r] two would produce a great advancement i[n] knowledge or originate a great thought in 2[5] years, but one great discovery, like that c[f] natural radiation, or x ray the vacuum tub[e] solid state, telegraphy, radio, television rada[r] penicillin, or sympathetic ganglionic blockin[g] agents, would more than justify the cost t[o] Americans America should and can afford t[o] support both types of investigations, technologi[c] and venture Technologic research is important of course but it is the spin off of the grea[t] advancements and discoveries made by a fe[w] creative thinkers The world needs more creati[ve] thinkers

Surely, there would be a problem in selecting o[r] recognizing the potential creative thinkers. Th[e] problem can be resolved but the process o[f] resolution could ruin the concept if it is not don[e] properly Maybe it is best to let the creativ[e] thinkers come forward on their own The larg[e] grant managers are not very likely to be amon[g] them since those are more business people— em pire builders to use a cliche Of course, some wh[o] receive contract support are really technolog ists and are also important Nevertheless it i[s] unfortunate that strictly venture research grant[s] based on confidence in the scientist alone ar[e] rarely supported A purely personal grant, a grant to an individual to do anything of investi gative nature, is hearsay today An application for such a grant in America would probably be completely disregarded How can a scientist describe in advance exactly what he plans to do if he doesn t know himself? And how can a creative thinker know in advance (before he starts to think) what he will think about, or what direction his thoughts will take or what he will attempt to investigate?

Fortunately some people think without financial support and some people just cannot avoid thinking creatively Maybe the best that America can do is to hope that there are enough of these silent dedicated thinkers who will work in their homes and garages without support with their results eventually reaching others to be developed technologically An important and great advancement in biomedical knowledge is truly rare but the venture research that produces it needs fostering

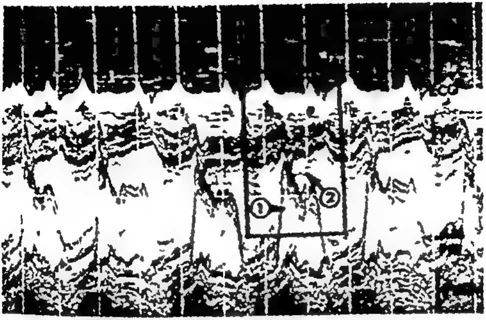

Fig 1A. Echocardiogram of a 15-year-old girl with aortic regurgitation showing diastolic flutter of the mitral valve and ventricular septum. The anterior mitral leaflet exhibits both coarse and fine oscillations. Arrow No 1 points to mitral flutter and arrow No 2 to septal flutter *VS* ventricular septum *AM* anterior mitral leaflet *PM* posterior mitral leaflet *PWLV* posterior wall of left ventricle

Results

A fine fluttering or vibratory motion was visible on the left side of the VS in 12 out of a total of 45 patients, matching fine flutter of the anterior mitral leaflet in frequency of oscillation In six of these 12 it was of slight degree restricted to early diastole and found only on the high VS (at the level of the free edge of the anterior mitral leaflet in diastole) Of the other six patients the septal flutter was holodiastolic and of greater degree involving the full septal thickness in four in these four septal flutter was visible over the lower (distal) septum although of lesser degree than on the higher septum In the remaining two patients it was seen only on the left aspect of the VS the duration of flutter varying from holodiastolic (over the high septum) to early diastolic (over the distal or lower septum)

Aortography was performed in 19 of the 45 patients and confirmed incompetence of the aortic valve The patients were divided into two categories according to the direction of the regurgitant jet as viewed in the left anterior oblique projection. In the first group composed of 12 patients the main jet or a major component of the broad fan shaped jet was directed anteriorly so as to impinge upon the VS Septal flutter was present in seven of these 12 patients In the

Fig 1B Magnification of the area indicated by arrows Nos 1 and 2.

Clinical communications

Flutter of left ventricular structures in patients with aortic regurgitation, with special reference to patients with associated mitral stenosis

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We have found that fine fluttering or vibratory motion of the ventricular septum (VS) in echo cardiograms of patients with the diastolic murmur of aortic regurgitation (AR) correlates well with the presence of an anteriorly directed regurgitant jet seen on aortography In addition we have observed anterior mitral valve leaflet flutter (mitral flutter) in two out of four patients with AR and associated stenotic mitral valves Mitral flutter is rarely reported in the presence of this combination of valvular lesions [1, 2]

Certain additional aspects of mitral and VS flutter due to AR, especially with coexisting mitral stenosis (MS) have hitherto escaped close attention The fixed duration of mitral flutter but not of VS flutter during diastolic periods of varying length in patients with AR and MS is one such observation being reported in this communication

Methods

Echocardiography was performed in 45 patients with AR who ranged in age from 9 to 74 years The diagnosis was based on the ausculta tion of a typical decrescendo basal early diastolic murmur Phonocardiography, done in most of the patients, confirmed the presence of such a murmur Associated MS was present in four cases and discrete fixed subvalvular aortic stenosis in one case Aortic systolic murmurs were usually present but clinically significant aortic valvular stenosis with two exceptions was absent or minimal in these patients Two patients had prosthetic aortic valves and three had prosthetic mitral valves

All echocardiograms were obtained on a Picker Echoview 10 ultrasonoscope connected to a strip chart Honeywell Visicorder Echoes from the mitral valve aortic valve, and the VS were obtained by standard techniques [3, 5] The echoes of the anterior and posterior leaflets of the mitral valve were examined for the presence of diastolic flutter Mitral flutter movements were studied with respect to (1) amplitude which was esti mated by subtracting the thickness of the leaflet (best seen in systole) from the maximum appar ent span of oscillation of the fluttering valve in diastole (2) duration, by examining the echo of the anterior leaflet of the mitral valve during diastole and (3) frequency of vibrations per second by using a ×10 magnifying loupe

The VS echo at different levels from high VS (at mitral valve level) to low VS (between mitral valve and apex), was examined for the presence of flutter Septal flutter was studied with respect to duration frequency and amplitude (slight, mod erate, marked)

Cineangiograms of aortic root injections obtained in 19 of the 45 patients were examined[4] with particular attention to the direction of the regurgitant jet and the degree of AR

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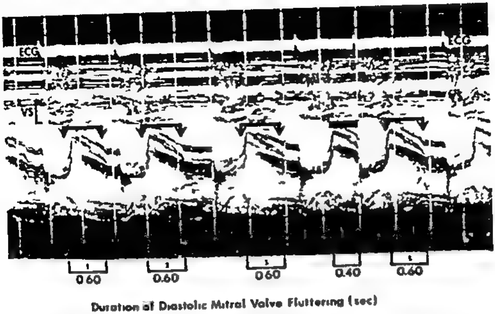

Fig 3 Echocardiogram of a 50-year-old woman with aortic regurgitation and mitral stenosis. The anterior mitral leaflet shows a fine diastolic flutter In the first three beats, with long diastolic periods, the mitral flutter ceases abruptly about 0 6 sec. after the *E* point.

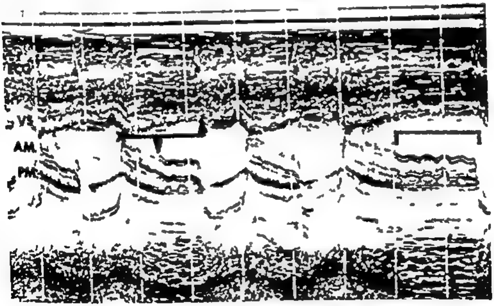

Fig 4 Echocardiogram of a 53-year-old man with aortic regurgitation and mitral stenosis A fine flutter is seen on the left aspect of the ventricular septum throughout diastole A similar flutter is evident on the anterior mitral leaflet but in the second and fourth beats (which have long diastolic periods) the mitral flutter ceases abruptly about 0.5 sec. after the *E* point. In the second beat *X* indicates the beginning of mitral and septal flutter the arrow pointing downward marks the termination of mitral flutter whereas septal flutter terminates much later at end diastole (arrow pointing upward) Slow oscillations (approximately 6 per sec) of the mitral valve due to atrial flutter fibrillation are particularly well seen in the last beat (bar)

mitral flutter begin simultaneously (*X*) but mitral flutter ends early (downward pointing arrow) whereas septal flutter persists until the end of diastole (upward pointing arrow) Also the coarse undulations of the anterior leaflet of the mitral valve that have been attributed to atrial fibrillation (bracket) differ significantly from the fine fluttering associated with AR In two patients with calcification of the mitral annulus (but not MS) typical flutter was evident on the

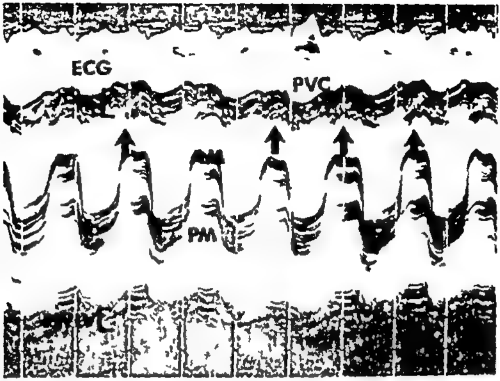

Fig 2 Echocardiogram of a 30-year old woman with aortic regurgitation and mitral stenosis A fine diastolic flutter is visible on the left aspect of the ventricular septum but not on the mitral valve Septal flutter is present during the whole of diastole including the longer postextrasystolic diastolic periods PVC premature ventricular contraction The arrows indicate septal flutter

second group of seven patients the regurgitant jet was directed centrally or posteriorly away from the septum Septal flutter was not seen in these cases Thus in those patients who were studied by aortography, septal flutter was associated invariably with an anteriorly directed aortic regurgitant jet whereas none of the patients with posteriorly directed jets demonstrated VS flutter No correlation was found between severity of aortic regurgitation and amplitude of mitral flutter

Forty of the 42 patients without mitral valve prosthesis showed a fine flutter of the anterior mitral leaflet The amplitude of this flutter varied from 3 to 7 mm, with an average of 4 4 mm Although usually of greatest amplitude in early diastole, the flutter was holodiastolic in all except in the four patients with associated MS two of whom had only early mitral flutter and the remaining two no mitral flutter at all The frequency of the flutter varied from 70 to 260 cycles per second In three cases in sinus rhythm a much coarser, irregular, and slower undulation was superimposed on the fine flutter (Fig 1) The thickness of the anterior mitral leaflet (measured during systole) varied from 1 to 4 mm with a mean of 2 0 mm Thirty five of the 42 also showed flutter of the posterior mitral leaflet which was always of lesser amplitude than that of the anterior leaflet in the same patient The seven patients in whom posterior leaflet flutter was not seen included two in whom the leaflet echoes could not be recorded and the four with MS Diastolic flutter of anterior chordae tendineae was noted in one patient and of posterior chordae in two others

In the four patients with MS the mitral leaflets showed echoes suggestive of sclerotic or calcific changes, the E F slope of the anterior leaflet was abnormally shallow and the posterior leaflet moved anteriorly during diastole instead of posteriorly as in the normal In two of the patients with MS septal flutter was marked, in the absence of mitral flutter (Fig 2) The third patient with MS had atrial fibrillation with cycle lengths varying from 0 70 to 1 78 sec When the cycle length was short and the diastolic intervals 0 60 sec or less the mitral flutter was holodiastolic but with longer lengths the vibratory motion of the anterior mitral leaflet was 0 60 sec in duration its cessation coincided with an abrupt decrease in E F slope (Fig 3) The echocardiogram of the fourth patient with MS, who was also in atrial fibrillation, showed a similar cessation of vibrations of the anterior mitral valve leaflet at the point of abrupt change of the diastolic slope (Fig 4) Fig 4 also demonstrates that septal and

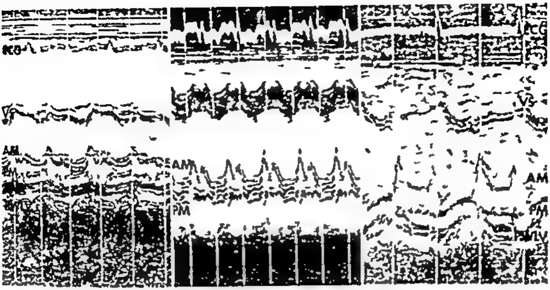

Fig 7 Mitral flutter in three patients with no auscultatory evidence of aortic regurgitation. Panel *A* shows the echocardiogram of a 60-year-old woman with mitral regurgitation and mitral annulus calcification. Panel *B* is the echocardiogram of a 58-year-old woman with mitral regurgitation and cardiomyopathy Panel *C* is the echocardiogram of a 66-year-old woman with severe anemia but no mitral regurgitation

flutter In the series of 75 patients of Pridie and associates,[2] rapid oscillation of the mitral valve in diastole, was present in 10 No fewer than 22 of 29 patients reported by Friedewald and associates[4] showed mitral flutter Cope and associates[1] recently reported 46 patients with AR who demonstrated mitral flutter of whom 17 showed VS flutter Forty of our 42 patients with AR (excluding three patients with mitral prostheses) exhibited rapid mitral oscillation of an amplitude of 3 mm or more The higher incidence of mitral flutter in the more recent reports could perhaps be attributed to different recording equipment Our findings are in agreement with those of Pridie and associates who remarked that no correlation existed between the severity of AR and the presence of mitral flutter We observed that the severity of mitral flutter was not proportional to the severity of AR as revealed by aortography

Diastolic mitral flutter was considered highly specific for AR by Winsberg and associates It is now becoming increasingly evident however that a similar fine vibratory motion of the mitral valve can occur in other types of heart disease including ventricular septal defects and right to left shunts [3] as well as in normal subjects We too have frequently encountered mitral flutter in the absence of AR particularly in patients with mitral regurgitation (Fig 7) In contrast to patients with aortic regurgitation who exhibit a greater amplitude of flutter on the anterior than posterior mitral cusp mitral flutter in patients without aortic regurgitation is more marked on the posterior mitral cusp

If the nonspecificity of mitral flutter as an echocardiographic sign of AR is confirmed by future experience the presence of septal flutter (which we have not observed in any condition other than AR) may assume greater diagnostic importance

Only one of nine patients in the series of Winsberg and associates[1] with combined MS and AR exhibited diastolic mitral flutter it was absent in all 20 of the patients with this combination of valvular lesions in the series of Pridie and associates[2] It is unlikely that thickening or sclerosis of the mitral leaflets alone is responsible for absence of flutter in MS because some of our patients without stenotic mitral valves had equally thickened (4 mm) cusps and yet showed typical mitral flutter Stiffness of the leaflets however may be a factor Two of our patients with MS and atrial fibrillation demonstrated flutter of the anterior mitral leaflet only in early and mid-diastole In one of these patients the duration of mitral flutter remained constant from beat to beat irrespective of cycle length in both

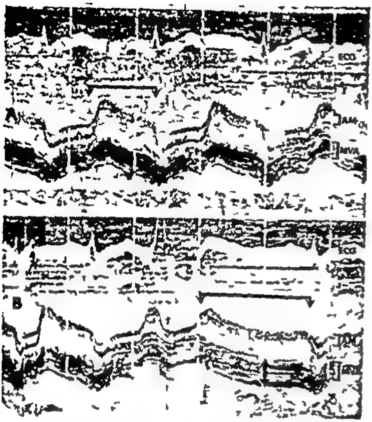

Fig 5 Echocardiogram showing diastolic flutter of the anterior mitral cusp in a 60 year old woman with aortic regurgitation (A) A calcified nonfluttering mitral annulus (*MVA*) is responsible for the broad dense echo situated posterior to that of the anterior mitral cusp which partly obscures the posterior mitral cusp The horizontal bar indicates the duration of mitral flutter (*B*) Fine flutter of the anterior mitral cusp continues throughout the prolonged diastole after a premature ventricular beat Cardiac catheterization in this patient proved the absence of mitral stenosis

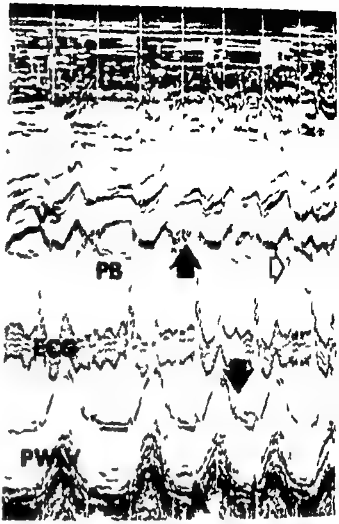

Fig 6 Echocardiogram of a 45 year old woman with a prosthetic Starr Edwards mitral valve The upper solid arrow indicates septal flutter the lower solid arrow left ventricular posterior wall endocardial flutter and the open arrow flutter of the prosthetic ball valve in diastole (faintly visible) *PB* posterior ball

mitral valve but not on the annulus (Fig 5)

Of the three patients with AR and a prosthetic mitral Starr Edwards valve early diastolic flutter of the ball and the septum was visible in two (Fig 6) One patient also exhibited fine flutter on the endocardium of the left ventricular posterior wall Aortography in this case demonstrated that a fan shaped regurgitant jet struck the VS anteriorly, the prosthetic mitral valve centrally and the posterior left ventricular wall posteriorly Aortography in another patient with a prosthetic mitral valve who exhibited septal flutter on echocardiography, revealed an anteriorly directed regurgitant stream Aortography was not performed in the third patient with mitral valve prosthesis Neither septal nor endocardial flutter was detected on echocardiography in 11 other patients with prosthetic mitral valves (but no aortic regurgitation) studied by us septal or endocardial flutter, in a patient with a prosthetic mitral valve thus appears a reliable sign of aortic regurgitation

Discussion

The echocardiographic appearance of diastolic flutter of the mitral valve in patients with AR was first described in 1966 by Joyner and associates[7] and further studied by Winsberg and associates[1] and Pridie and associates[2] It has proved a useful indirect sign of AR since the echo obtained from the aortic valve in this condition does not itself have any specific or constant diagnostic findings[3, 4, 5, 6]

Of 35 patients with clinical signs of AR without MS reported by Winsberg and co workers,[1] 11 had a characteristic fluttering motion of the anterior mitral leaflet' and five others had equivocal

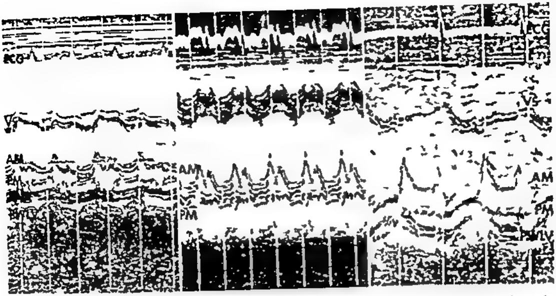

Fig 7 Mitral flutter in three patients with no auscultatory evidence of aortic regurgitation Panel *A* shows the echocardiogram of a 60-year-old woman with mitral regurgitation and mitral annulus calcification Panel *B* is the echocardiogram of a 28-year-old woman with mitral regurgitation and cardiomyopathy Panel *C* is the echocardiogram of a 66-year-old woman with severe anemia but no mitral regurgitation

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patients, cessation of mitral flutter occurred simultaneously with the end or an abrupt decrease of the E F slope, after the anterior mitral leaflet had moved to a partly closed position Continuation of VS flutter beyond this point (Fig 4) indicates that AR had not yet ceased The reason for the simultaneous end of mitral flutter and change in E F slope has not yet been established but two possible explanations may be considered (1) The marked decrease or reversal in diastolic pressure gradient between the left atrium and left ventricle produced by AR[14] may decrease the flow between the two to the extent that the stiff stenotic anterior leaflet of the mitral valve is no longer suspended in a vibrating state, between two streams of flow—that of left atrial emptying and the AR jet[15] (2) As ventricular pressure rises during diastole the anterior mitral valve leaflet, abnormally tethered to the posterior leaflet, moves posteriorly until it is no longer subject to the direct effects of the regurgitant jet In such a position the stenotic valve neither vibrates nor closes further during diastole

A fine diastolic vibration of the VS was noted in approximately one half of the patients with AR recently described by Friedewald and associates,[10] in one third of those of Cope and associates,[11] and in one fourth of ours Two recent reviews however devoted to echocardiography of the VS[12, 16] and another to valvular heart disease[1] make no mention of VS flutter The septal flutter of the high VS was restricted to early diastole in six of our patients, in these cases the vibrations were of small amplitude and detectable only on the left aspect of the VS In six other patients however, the septal flutter was of greater amplitude and longer duration, in four of these it extended throughout diastole involved the whole thickness of the high VS and existed even at low septal levels

Edwards and Burchell[18] in 1958 described local areas of endocardial thickening on the anterior mitral leaflet and on the VS which they called "jet" lesions They postulated that jet lesions may designate possible sites of origin of murmurs in whole or in part and in this regard may be utilized in the explanation of the particular positions of the maximal intensity of murmurs recorded during life Vibration of the VS may help to explain why the early diastolic murmur of AR is usually very well heard at the left lower parasternal region Based on our findings in a patients with a prosthetic mitral valve and aortic regurgitation we suggest that the mid diastolic and presystolic murmurs of the Austin Flint type that have been observed in such patients[19] may result from flutter of the ball of the artificial valve, the septum, or a combination of these Thus, echocardiography provides the clinician not only with a diagnostic aid but also with a means of understanding the genesis of some auscultatory signs

Aortography showed that part or all of the regurgitant jet was directed anteriorly toward the VS in all patients with septal flutter, and toward the central portion or posterior wall of the left ventricular chamber in patients without septal flutter The absence of septal flutter in some patients with AR directed anteriorly would suggest that other factors, such as velocity of the regurgitant jet might also play a role in determining the presence or absence of septal vibration

Thus, as an echocardiographic sign of an aortic leak VS flutter is less frequently encountered than mitral flutter and is related to an anteriorly directed aortic regurgitant jet VS flutter may be more specific, however, and in the presence of MS, flutter of the VS may be present alone (as in two of our patients), or may be of greater amplitude and duration than that of the mitral valve The cessation of mitral flutter in mid diastole in patients with MS simultaneous with an abrupt decrease in E F slope, is an intriguing finding that requires further study with hemodynamic and angiocardiographic correlations

Summary

Echocardiography was performed in 45 patients with aortic regurgitation Forty showed a high frequency diastolic flutter of the mitral valve which was holodiastolic in all but the patients with associated mitral stenosis

Of four patients with coexisting mitral stenosis mitral flutter was absent in two, in the other two, in atrial fibrillation mitral flutter occurred but only during a fixed interval after mitral valve opening irrespective of cycle length

A fine flutter of similar frequency was observed on the left ventricular aspect of the ventricular septum in 12 patients In six of these it was of slight degree and restricted to early diastole and the high septum in four others (three of whom had associated mitral stenosis), the septal flutter

was more marked holodiastolic and present over all parts of the septum scanned, in two it was holodiastolic over *the high septum but early* diastolic at lower septal levels

Aortography performed in 19 patients showed that septal flutter was present in seven of 12 patients in whom the regurgitant aortic jet was directed forward to the ventricular septum, whereas in the other seven patients with no septal flutter, the jet was directed away from the septum. Septal flutter is useful as an echocardiographic sign of aortic regurgitation especially in the presence of mitral stenosis when mitral flutter may be absent or exceeded by septal flutter in both amplitude and duration and when the mitral valve has been replaced by a prosthetic valve Vibration of the septum appears to be attributable to the regurgitant aortic jet impinging on it and may contribute to the production and radiation of the characteristic diastolic murmur of aortic regurgitation

REFERENCES

1. Winsberg F Gabor E. F and Hernberg J G Fluttering of the mitral valve in aortic insufficiency Circulation 41 225 19 0
2. Pridie, R. B Benham R., and Oakley C M Echocardiography of the mitral valve in aortic valve disease Br Heart J 33 291 1971
3. Gramiak, R., and Shah, P M Echocardiography of the normal and diseased aortic valve Radiology 91 1 19 0
4. Hernberg, J Weiss, B and Keegan A. The ultrasonic recording of aortic valve motion Radiology 94 361 1970
5. Feigenbaum, H Echocardiography Philadelphia 1972 Lea & Febiger Publishers, p 37
6. Hunt, D Baxley W A Kennedy J W Judge T P Williams, J E. and Dodge H T Quantitative evaluation of cineaortography in the assessment of aortic regurgitation Am J Cardiol. 31 696 1973
7. Joyner C R. Dyrda, L., Barrett, J and Reid J M Behavior of the anterior leaflet of the mitral valve in patients with Austin Flint murmur Clin Res. 14 251 1966
8. Feizi, O Symons, C., and Yacoub M Echocardiography of the aortic valve I Studies of normal aortic valve or aortic stenosis, aortic regurgitation and mixed aortic valve disease Br Heart J 36 341 1974
9. Castillo-Fenoy A Houeix, J M., Veber G., Klepacki, Piwnica, A., and Tricott R. L échocardiographie dans les valvulopathies aortiques Arch. Mal Coeur 67 82, 1974
10. Friedewald V E., Futral, J E., Kinard S S., and Phillips, V Oscillations of the interventricular septum in aortic insufficiency (abst.) J Clin Ultrasound Suppl p. 60 1974
11. Cope G D Kisslo J A Johnson, M L., and Myers, S., Diastolic vibration of the interventricular septum in aortic insufficiency Circulation 51 589 1975
12. Assad Morell, J L., Tajik, A J., and Giuliani, E R Echocardiographic analysis of the ventricular septum Prog. Cardiovasc Dis. 17 219 1974
13. Goldberg, S J Allen H D., and Sahn D Pediatric and adolescent echocardiography Chicago 1975 Year Book Medical Publishers, Inc., p. 99
14. O Brien, K. P., and Cohen, L. S Hemodynamic and phonocardiographic correlates of the Austin Flint murmur Am. Heart J 77 603 1969
15. Ross, R. S and Criley J M Cineangiocardiographic studies of the origin of cardiovascular physical signs, Circulation 30 255 1964
16. Sawaya, J., Longo, M R., and Schlant R. C Echocardiographic interventricular septal wall motion and thickness A study in health and disease, Am Heart J 87 681 1974
17 Teichholz, L. E. Echocardiography in valvular heart disease Prog. Cardiovasc Dis. 17 281 1975
18. Edwards, J E. and Burchell H B Endocardial and intimal lesions (jet impact) as possible sites of origin of murmur Circulation 18 946, 1958
19. Schaetter R. A., McAnulty J H Starr A., and Rahimtoola, S. Diastolic murmurs in the presence of Starr Edwards mitral prosthesis With emphasis on the genesis of the Austin Flint murmur Circulation 51 402, 1975

Hypoxemia and lung water in acute myocardial infarction

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Hypoxemia is recognized as a frequent consequence of acute myocardial infarction [1-9] Previous investigation has determined that increasing severity of left ventricular failure is accompanied by progressively more severe hypoxemia [1,3,5,7] Pulmonary wedge pressure (Pw) in acute myocardial infarction has been found to correlate with the level of hypoxemia suggesting that increased hydrostatic pressure leading to pulmonary interstitial edema is at least in part responsible for the abnormality [4,5] Actual measurements of pulmonary extravascular lung water have been found to be elevated in patients with left ventricular failure [10,11]

This study was undertaken to demonstrate the relationship between arterial hypoxemia hemodynamic dysfunction, and extravascular lung water in acute myocardial infarction

Materials and methods

Eighty eight patients with acute myocardial infarction were studied in the Myocardial Infarction Research Unit (MIRU) of the University of Rochester Medical Center The diagnosis of acute myocardial infarction was based upon a typical history serial enzyme changes and specific electrocardiographic (ECG) criteria [10] Patients were classified in three groups Class I, no ventricular gallop or pulmonary rales, Class II, ventricular gallop and basilar rales, Class III, pulmonary edema (marked dyspnea ventricular gallop, and pulmonary rales over the lower half of the chest) Patients in cardiogenic shock were excluded from this study for blood gas analysis off oxygen therapy was not advisable in this critically ill group Those patients suspected of having chronic lung disease were also excluded Informed consent was obtained from each patient

Following admission to the MIRU a No 5 or No 7 Swan Ganz flow directed catheter was advanced to the main pulmonary artery via an antecubital vein under local anesthesia and fluoroscopic control [11] An 18 gauge Teflon cannula was placed in a brachial artery for measurement of systemic arterial pressure and for blood sampling

Pulmonary artery pulmonary wedge, and brachial artery pressures were measured with Statham Model SP37 transducers and recorded on a Brush direct writing recorder Mean pressures were obtained by electronic integration Zero reference level for pressure measurements was 5 cm below the sternal angle

Patients either breathed room air or were removed from oxygen therapy for at least 15 minutes before sampling of blood from the brachial artery for measurement of blood gases Determinations of Po_2, Pco_2 and pH were made

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with an IL 113-02 Micro pH/blood gas system * All values were corrected for variation in body temperature

Cardiac output was measured by the indicator dilution technique with indocyanine green dilution curves. Arterial blood was continuously withdrawn from the brachial artery by a Harvard pump and through a Gilford cuvette densitometer at the rate of 45 9 ml per minute A rapid injection of 3 ml (7.5 mg) of indocyanine green into the pulmonary artery was rapidly followed by a saline flush Analogue to digital conversion of the indicator dilution curves was performed on line at a rate of 160 samples per second by an XDS Sigma 3 computer The computer averaged the 16 time-concentration values obtained during each 0 1 second and the values were used to calculate cardiac output with the gamma variate technique.[8] In each patient two to four determinations of cardiac output were made in rapid succession and the reported value represents an average of these measurements After each determination, withdrawn blood was reinfused under sterile technique to avoid excessive blood loss

Within 10 minutes after completion of pressure measurements and cardiac output determinations, pulmonary extravascular volume (PEV) was measured once in each patient PEV or lung water was determined by a double radioisotope technique previously described from our laboratory [9]

PEV was calculated according to the following formula

$$PEV = \frac{CI}{60}\left[\bar{T}m_{THO(PA-BA)} - \bar{T}m_{RISA(PA-BA)}\right]$$

Where

PEV = pulmonary extravascular water volume (ml /M)

CI = cardiac index (ml /min /M)

$\bar{T}m_{THO(PA-BA)}$ = mean transit time of tritiated water from pulmonary artery to brachial artery (sec)

$\bar{T}m_{RISA(PA-BA)}$ = mean transit time of radio iodinated serum albumin from pulmonary artery to brachial artery (sec)

In this formula it is implied that the expression

$$\frac{CI}{60} \times \bar{T}m_{RISA(PA-BA)}$$

represents the distribution volume of water in blood Since blood is heterogeneous and contains elements other than water this assumption may be incorrect The water fraction of plasma and that of red cells is not the same so the water content of whole blood would naturally be influenced by the number of red cells or hematocrit The PEV may be overestimated because of the difference in plasma and red cell water fractions. A correction factor of 0 8 was used as suggested by Chinard and associates[10] All the values of PEV determined in this series of patients were corrected by multiplying by this factor of 0 8 and were expressed in terms of square meters of body surface area None of the 88 patients had a significant reduction in hematocrit

The reproducibility of the technique was established by duplicate determinations of PEV carried out 30 minutes apart in eight other patients revealing a variability of 11 per cent or less. The upper limit of normal value in our laboratory is 120 ml per square meter with a mean normal value of 90 ml per square meter Hemodynamic study was carried out at varying stages of illness on the first to seventh day of hospitalization The majority of patients were studied within 48 hours of onset of infarction

An unpaired t test was used to compare the differences between groups of patients Correlation coefficients between various parameters were calculated with standard techniques[11]

Table I Patient population location of infarction and clinical class

Patient population	
Age 30 to 77 years (mean 56)	
Sex, 74 men, 14 women	
Location of myocardial infarction	
Anteroseptal	30
Anterolateral	15
Diaphragmatic	35
Subendocardial	8
Clinical class	
I (no ventricular gallop or pulmonary râles)	50
II (ventricular gallop and basilar râles)	27
III (pulmonary edema)	11

Results

The patient population is outlined in Table I There were 74 men and 14 women, ranging in age from 30 to 77 with a mean age of 56 years Thirty

*Instrumentation Laboratory Inc 113 Hartwell Ave Lexington Mass 02173.

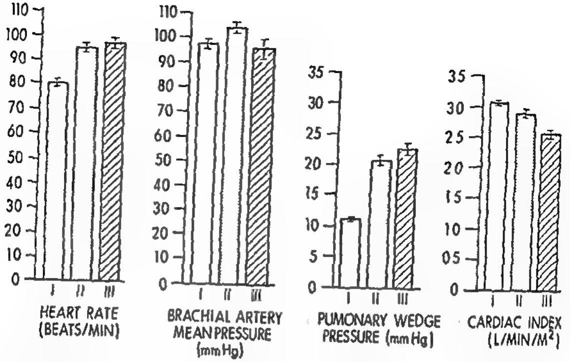

Fig 1 Hemodynamic data according to clinical class in 88 patients with acute myocardial infarction Brackets indicate standard error of the mean

Table II Differences between clinical classes in selected hemodynamic parameters

HR	*BAm*	*Pw*	*CI*	*PEV*
Class I II ($p < 0.05$) I III ($p < 0.05$) II III (NS)	Class I II (NS)* I III (NS) II III (NS)	Class I II ($p < 0.05$) I III ($p < 0.05$) II III (NS)	Class I II (NS) I III ($p < 0.05$) II III (NS)	Class I II ($p < 0.05$) I III ($p < 0.05$) II III ($p < 0.05$)

NS No statistical significance

patients had anteroseptal myocardial infarction (MI), 15 patients had anterolateral MI, 35 patients diaphragmatic MI, and eight patients had subendocardial MI Fifty patients were considered in Class I, 27 in Class II, and 11 in Class III The data collected and arranged according to clinical class appear in Fig 1 The significance among various parameters and the correlation coefficients are listed in Tables II and III

Heart rate Mean heart rate (HR) increased significantly ($p < .05$) between Classes I and II I and III, but not between II and III

Brachial artery pressure There was no significant difference in brachial artery mean pressure (BAm) between groups

Pulmonary wedge pressure Pulmonary wedge pressure (Pw) progressively increased according to clinical class The difference was statistically significant between Classes I and II and I and III ($p < 0.05$) No significant difference existed between Classes II and III

Cardiac index Cardiac index (CI) progressively decreased according to clinical class The difference was of statistical significance only between Classes I and III ($p < 0.05$)

Pulmonary extravascular volume or lung water The measurements of extravascular volume or lung water appear in Fig 2 The mean values progressively increased in amount with increasing severity of left ventricular failure as judged by clinical class Class I, 126 ml per square meter Class II 153 ml per square meter, Class III 228 ml per square meter The difference in mean values for each group was statistically significant ($p < 0.05$)

Arterial oxygen tension The values of arterial Po_2 determined according to clinical class appear in Fig 3 A progressive decrease in Pa_{O_2} was observed with increasing clinical evidence of left ventricular failure The difference was statistically significant at $p < 0.05$ level only between Classes I and III

A significant correlation was found between

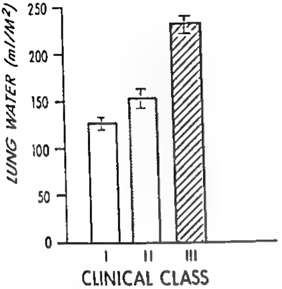

Fig. 2 Lung water according to clinical class. Brackets indicate standard error of the mean

PEV and (1) heart rate ($r = 0.29$ $p < 0.01$) (2) pulmonary wedge pressure ($r = 0.47$ $p < 0.01$) and (3) arterial oxygen tension ($r = -0.26$, $p < 0.02$) (see Table III) Likewise arterial oxygen tension was correlated with (1) pulmonary wedge pressure ($r = -0.28$ $p < 0.01$) and (2) heart rate ($r = -0.25$ $p < 0.05$)

The relationship between pulmonary wedge pressure and lung water is depicted in Fig 4 As the wedge pressure increased so did the lung water When the wedge pressure was compared to arterial Po a negative correlation was noted (Fig 5) Progressively increasing wedge pressure was accompanied by decreasing arterial Po A similar negative relationship was found between lung water and hypoxemia (Fig 6) With increasing lung water arterial Po_2 decreased

Discussion

Previous studies have shown that measurements of hemodynamic performance in acute myocardial infarction are useful in determining degrees of left ventricular dysfunction [3, 22] Despite some uncertainty regarding an elevated pulmonary wedge pressure as representative of compliance changes in the left ventricle versus true left ventricular failure acute elevation of the pulmonary wedge pressure suggests impairment of myocardial function A single measurement of cardiac output may not be meaningful yet when analyzed in a serial fashion and in relation to

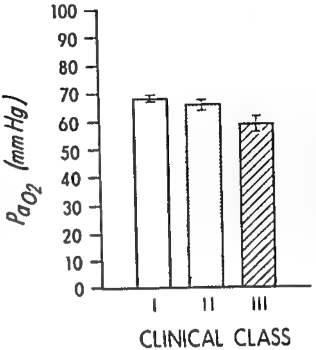

Fig 3 Arterial Po according to clinical class. Brackets indicate standard error of the mean.

Table III Correlation coefficients

	HR	*BAm*	*Pw*	*CI*	*Pa_O*	*PEV*
HR	–	0 10	0.2 †	0 20	–0.25‡	0 29
BAm	0 10	–	0 21	–0 04	0 00	–0 08
Pw	0 2 †	0.21	–	–0 23‡	–0 28	0 4
CI	0 20	–0 04	–0.23‡	–	0 13	0 08
Pa_O	–0 25‡	0 00	–0.28	0 13	–	–0 26†
PEV	0 29	0 08	0 47	0 08	–0 26†	–

p < 0 01
†p < 0 02
‡p < 0 05

pulmonary wedge pressure knowledge of cardiac output is of prognostic and therapeutic value [23, 2]

This study has shown that with increasing clinical evidence of left ventricular failure certain hemodynamic parallels can be drawn The heart rate and pulmonary wedge pressure were higher and cardiac index lower in patients with pulmonary rales and a ventricular gallop than those without Between Class I and Class II patients only changes in heart rate and pulmonary wedge pressure reached statistical significance ($p < 0.05$) Comparing Class I and Class III patients a statistically significant difference was observed in heart rate pulmonary wedge pres

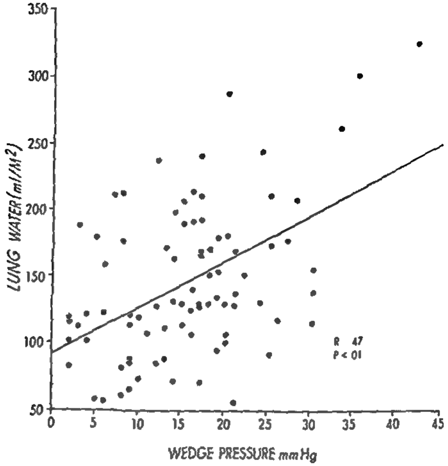

Fig 4 The relationship of pulmonary wedge pressure and lung water The dotted lines represent confidence bands.

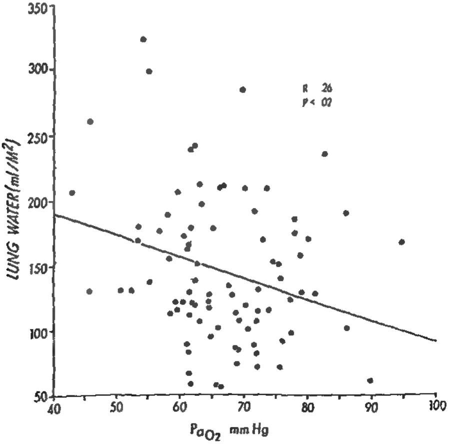

Fig 5 The negative relationship between lung water and arterial Po The dotted lines represent confidence bands.

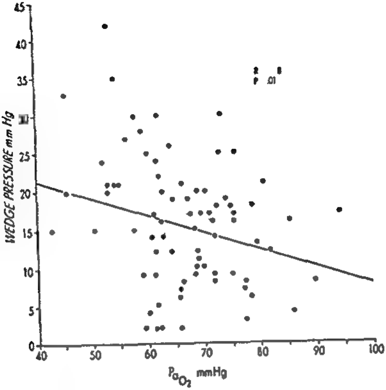

Fig 6 The negative relationship between wedge pressure and arterial Po The dotted lines represent confidence bands.

sure and cardiac index ($p < 0.05$) Systemic blood pressure however did not vary with clinical class. When contrasting degrees of left ventricular failure (Class II vs Class III) there was no difference of statistical significance in any of the following parameters heart rate systemic blood pressure pulmonary wedge pressure or cardiac index Clinical assessment of patients therefore is a relatively insensitive measure of degrees of severity of hemodynamic derangement within the group with left ventricular failure The measurement of lung water however was significantly different for each clinical class ($p < 0.05$) In addition lung water was directly related to the level of pulmonary wedge pressure As depicted in Fig 4 a linear relationship exists between pulmonary wedge pressure and lung water ($r = 0.47$ $p < 0.01$) Neither cardiac index nor systemic blood pressure was related to the amount of lung water Thus increased hydrostatic pressure in the pulmonary bed secondary to pulmonary venous hypertension appears to be a major determinant of pulmonary edema in acute myocardial infarction

Arterial hypoxemia has been recognized as a frequent occurrence in acute myocardial infarction • The degree of hypoxemia has been found to correlate relatively well with the clinical assessment of left ventricular failure and the level of pulmonary wedge or pulmonary artery diastolic pressure • Abnormal oxygenation however has been reported even in the absence of clinical or radiologic evidence of left ventricular failure • • The mechanisms possibly responsible for hypoxemia in acute myocardial infarction include (1) alveolar hypoventilation (2) diffusion abnormalities and (3) ventilation perfusion imbalances with increased arteriovenous shunting

Alveolar hypoventilation is an unlikely mechanism of hypoxemia because CO retention is rarely present Diffusion abnormalities however have been demonstrated in left ventricular failure and likely contribute to hypoxemia Pulmonary arteriovenous shunting also occurs in acute myocardial infarction and the degree of shunting is correlated with diminished Pa_{O_2} •

Some investigators have shown that closing volume increases in patients with congestive heart failure as a consequence of increased interstitial pressure resulting from increase in both

pulmonary vascular pressure and lung water[2,27]

Hales and Kazemi have recently demonstrated small airway dysfunction by abnormal "closing volumes" in acute myocardial infarction in the absence of obvious myocardial failure[9] They postulate that even transient left ventricular failure in clinically uncomplicated patients may lead to interstitial edema, premature airway closure, and hypoxemia On the other hand, improvement of pulmonary function, including airway change has been demonstrated in patients with chronic uremia in whom removal of excess lung water was accomplished by hemodialysis[28]

In the present study, arterial oxygen tension varies with clinical class, the most severe abnormalities accompanied greater degrees of left ventricular failure Hypoxemia was present in our Class I patients without clinical or hemodynamic evidence of left ventricular failure The mean value of lung water of 126 ml per square meter in this group is only slightly greater than the top limit of normal of 120 ml per square meter in our laboratory Thus hypoxemia may occur in acute myocardial infarction without major abnormalities of left ventricular function or excessive accumulation of interstitial fluid in the lungs As both wedge pressure and lung water increased arterial Po decreased The relationships are of statistical significance These data would suggest therefore that arterial hypoxemia is related to an elevation in pulmonary wedge pressure and the subsequent increase in extravascular lung water but the relationships are not necessarily linear[29,30] As demonstrated by Hales and Kazemi[9] small airway dysfunction may be an important factor to produce hypoxemia in acute myocardial infarction uncomplicated by obvious left ventricular failure Pulmonary edema in dependent areas of the lung can result in redistribution of flow to upper lobes of the lung[31,32] Thus perfusion of better ventilated upper lobes could reduce the degree of hypoxemia expected with more severe pulmonary edema

The present study has shown that increased pulmonary hydrostatic pressure in patients with acute myocardial infarction is probably a major factor in transportation of fluid into the pulmonary interstitial space As lung water increases, arterial oxygenation decreases However, a quantitative relationship between the amount of interstitial fluid and degree of hypoxemia cannot be established The mechanism of hypoxemia in the presence of the excessive lung water may be due to both small airway dysfunction from premature closure and intrapulmonary shunting

Summary

Pulmonary extravascular volume or lung water (PEV), arterial blood gases, and cardiac hemodynamics were measured in [redacted] patients with acute myocardial infarction A progressive increase in PEV and a decrease in arterial oxygen tension (Pa_{O}) were observed from Class I (uncomplicated) patients to Class III (frank pulmonary edema) patients Heart rate and pulmonary wedge pressure (Pw) rose and cardiac index declined with increasing severity of heart failure by clinical classification

There was a significant correlation between PEV and Pw independent of clinical class ($r = 0.47$, $p < 0.01$) Pa_{O_2} had a negative correlation with Pw ($r = -0.28$ $p < 0.01$) as well as PEV ($r = -0.26$ $p < 0.02$)

We conclude therefore that increased pulmonary hydrostatic pressure secondary to pulmonary venous hypertension in patients with acute myocardial infarction is a major determinant of interstitial edema At higher values of PEV, Pa_{O} was lower The mechanism of hypoxemia in the presence of excessive lung water may be due to multiple factors including small airway dysfunction and intrapulmonary shunting

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REFERENCES

1 Valencia A and Burgess J H Arterial hypoxemia following acute myocardial infarction Circulation 40 641 1969
2 Fillmore S J Shapiro M and Killip T Arterial oxygen tension in acute myocardial infarction Serial analysis of clinical state and blood gas changes Am Heart J 79 620 1970
3 Ramo [redacted] W Myers N Wallace A G Starmer F Clark D O and Whalen R E Hemodynamic findings in 123 patients with acute myocardial infarction on admission Circulation 42 567 1970
4 Lassers B W George M Anderton J L Higgins, [redacted] R and Philip T Left ventricular failure in acute myocardial infarction Am J Cardiol 25 511 1970
5 Fillmore S J Guimaraes A C Scheidt S S and Killip T Blood gas changes and pulmonary hemody

namics following acute myocardial infarction Circulation 45:563, 1972.
6. Wolk, M. J Scheidt S and Killip T Heart failure complicating acute myocardial infarction Circulation 45 1125, 1972.
7. Interiano, B., Hyde R. W Hodges M., and Yu P N Interrelation between alterations in pulmonary mechanism and hemodynamics in acute myocardial infarction J. Clin. Invest. 52 1994 1973
8. Rebuck, A. S., Cade J F., and Campbell E J M Pulmonary aspects of myocardial infarction Mod. Conc Cardiovasc. Dis. 42 17 1973.
9. Hales, C. A., and Kazemi H Small airways function in myocardial infarction, N Engl. J Med 290 761 1974
10. Lilienfield, L. S Ernie E D., Partenope E A and Morowitz, H. J Transcapillary migration of heavy water and thiocyanate ion in the pulmonary circulation of normal subjects and patients with congestive heart failure, J Clin. Invest. 34 1 1955
11. McCredie, M. Measurement of pulmonary edema in valvular heart disease Circulation 36 381 1967
12. Turino, G M Edelman, N H Senior R M Richards, E C and Fishman A. P Extravascular lung water in cor pulmonale Bull. Physiopathol. Respir 4 47 1968
13. Yu, P N Lung water in congestive heart failure Mod. Conc. Cardiovasc. Dis. 40 27 1971
14. Biddle T L., Khanna P K Yu P N Hodges, M and Shah, P M.. Lung water in patients with acute myocardial infarction Circulation 49 115 1974
15. Sutherland, P W., Cade J F., and Pain M C F Pulmonary extravascular fluid volume and hypoxaemia in myocardial infarction Aust. N Z. J Med 1 141 1971
16. Criteria adopted by the Myocardial Infarction Research Units, National Heart and Lung Institutes 1969
17. Swan, H. J C Ganz, W Forrester J Marcus H Diamond, G and Chonette D Catheterization of the heart in man with use of a flow-directed balloon tipped catheter N Engl J Med 283 447 1970
18. Thompson, H. K Jr Starmer C F Whalen, R E and McIntosh, H. D Indicator transit time considered as a gamma variate Circ. Res. 14 502 1964
19. Schreiner B F Jr Murphy G W Shah P M Kramer D H and Yu P N Pulmonary extravascular volume in cardiac patients, Circulation 44(Suppl. II) 39 1971
20. Chinard F P., Perl, W., Effros, R M., Dumpys, R., and Delea, A. C Lung water Physiological and clinical significance Trans. Am Clin Climatol Assoc 81 85 1969
21. Snedecor G W and Cochran W G Statistical methods, ed 6, Ames, Iowa 1967 State University Press.
22. Rahimtoola S H Loeb H S., Ehsani, A., Sinno M Z., Chuquimia, R., Lal R., Rosen K M and Gunnar R Relationship of pulmonary artery to left ventricular diastolic pressures in acute myocardial infarction Circulation 45 283, 1972.
23. Ratshin R. A., Rackley C E., and Russell R O Jr Hemodynamic evaluation of left ventricular function in shock complicating myocardial infarction Circulation 45 127 1972.
24. Rackley C E., and Russell R O Jr Left ventricular function in acute myocardial infarction and its clinical significance, Circulation 45 231 1972.
25. Hughes, J M B Pulmonary interstitial pressure Bull Physiol. Pathol. Respir 7 1095 1971
26. Turino G M., Pine, M B., Shurbroodas, S J., and Casey J P The volume of extravascular water of the lung in normal man and in disease Bull Physiol Pathol Respir 7 1161 1971
27. Milic Emili, J., and Ruff F Effects of pulmonary congestion and edema in the small airways, Bull. Physiol. Pathol. Respir 7 1181 1971
28. Zidulka, A., Despas, P J., Milic Emili, J., and Anthonisen N R. Pulmonary function with acute loss of excess lung water by hemodialysis in patients with chronic uremia Am. J Med. 55 134 1973
29. Guyton A. C., and Lindsay A W Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema Circ. Res. 7 649 1959
30. Levine O R., Mellins, R. B and Fishman A P Quantitative assessment of pulmonary edema Circ Res. 17 414 1965
31. West J B Dollery C T and Heard B E Increased pulmonary vascular resistance in the dependent zone of the isolated dog lung caused by perivascular edema, Circ. Res. 17 191 1965
32. Kazemi H Parsons, E F Valencia L M and Strieder D J Distribution of pulmonary blood flow after myocardial infarction and ischemia Circulation 41 1025 1970

A comparative analysis of pulmonary perfusion scans with pulmonary angiograms

FROM A NATIONAL COOPERATIVE STUDY

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For more than a decade, lung perfusion scans have been employed to evaluate patients with suspected pulmonary emboli When four views are obtained, a normal lung perfusion scan virtually excludes the diagnosis of pulmonary embolism[1] Numerous pathologic processes can alter pulmonary blood flow and therefore an abnormal scan is not diagnostic Pulmonary angiography rarely yields false positive results but may miss microemboli in the peripheral pulmonary vessels[2,3] Comparative studies of these techniques have stressed that they are complementary[4-7] Reported studies were completed, however before the widespread use of lateral scans, which are said to increase diagnostic accuracy[4] A comparison of lung scans and pulmonary angiograms, performed almost simultaneously in 162 patients with suspected pulmonary emboli admitted to a therapeutic trial on the basis of angiographic evidence of pulmonary embolism, forms the basis of this report

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Materials and methods

A total of 176 patients from 11 medical centers were studied in the period from 1970 to 1973[8]

Study criteria The patients in this report all had pulmonary embolism diagnosed by angiography Where possible, pulmonary lung perfusion scans were also performed before entrance into the study When done pulmonary lung perfusion scans were performed within 1 to 2 hours, either before or after the pulmonary angiogram In most instances the angiogram and the lung scan were performed within minutes of each other Verbal and written informed consent that was witnessed according to regulations of the Department of Health Education and Welfare were obtained from each patient

Technique The techniques of pulmonary angiography and lung perfusion scanning were performed as previously described[4] Specific details of the properties of the radiopharmaceuticals dose schedules methods of collimator calibration and film density for this study were previously reported[8]

Interpretation of angiograms and lung scans The pulmonary angiograms were sent separately to three radiologists with expertise in this area, who independently interpreted the study[8] Each expert was uninformed of the clinical history, patient identity and institution where the study was performed The experts interpreted the films

by two approaches, one subjective and one objective. The subjective method was composed of two categories

Diagnostic evaluation.

Massive pulmonary embolism. Presence of obstructions or significant filling defects involving two or more lobar pulmonary arteries or an equivalent number of defects in other vessels.

Submassive pulmonary embolism. Presence of obstruction or filling defect in at least one segmental pulmonary artery with the sum of defects being less than that for massive pulmonary embolism

Abnormal but not meeting the criteria for pulmonary emboli.

Normal pulmonary angiogram

Severity rating The severity rating was based on the radiologist s visual estimate of severity taking into account the amount size and location of clots, blood flow size of perfusion defects cardia size and radiographic appearance of uninvolved vessels. This rating was subdivided as follows.

Severe—awarded 3 points

Moderately severe—awarded 2 points.

Minimally severe—awarded 1 point

Normal—awarded no points

The objective method to quantify perfusion defects assigned a numerical index of extent of pulmonary emboli present and has been previously reported in detail.[6]

For inclusion in the therapeutic trial at least two of the three panel members had to be in agreement on the presence of pulmonary emboli.

The lung scans (anterior posterior right and left lateral views) accompanied by chest x rays were independently read by five recognized experts.[6] Each expert was unaware of the clinical history patient identity and institution where scan was performed They rated the quality of the study (excellent satisfactory unsatisfactory or noninterpretable) and made a diagnostic evaluation as follows

HIGH PROBABILITY OF PULMONARY EMBOLISM (1) Chest x ray No consolidation or evidence of obstructive pulmonary disease (2) Lung scan Single or multiple characteristic perfusion defects which do not correspond to abnormalities seen on chest x ray a changing pattern of defects on serial scans

Table I Consistency among lung scan panel*

	No	Per cent
Complete diagnostic agreement	50	31.5
One panelist disagreement with difference of one diagnostic category	42	25.9
One panelist disagreement with difference of two diagnostic categories	3	1.9
Two panelists disagreement with difference of one diagnostic category	[illegible]	19.1
Two panelists disagreement with difference of two diagnostic categories	12	7.4
Three panelists disagreement with difference of two or more diagnostic categories	23	14.2
Total cases in which more than one panelist disagreed and the difference ranged two or more diagnostic categories	35	21.6

*Of 162 patients in whom the scan was interpreted as positive 1[illegible]6 also had angiograms diagnostic of pulmonary emboli. There was no correlation between the scan panel agreement and the likelihood of a positive angiogram.

MEDIUM PROBABILITY OF PULMONARY EMBOLISM (1) Chest x ray No evidence of obstructive pulmonary disease (2) Lung scan Single or multiple areas of decreased perfusion which do not correspond to abnormalities seen on chest x ray however the position and shape of the defects are not sufficiently characteristic of pulmonary embolism to allow a diagnosis of high probability of pulmonary embolism

LOW PROBABILITY OF PULMONARY EMBOLISM Single or multiple perfusion defects are present on the lung scan but either (1) the size or shape of these defects is not sufficiently characteristic of pulmonary embolism or (2) another explanation e g obstructive pulmonary disease or roentgenographic abnormalities accounts for these defects.

NO EVIDENCE OF PULMONARY EMBOLISM Either the lung scan is normal or the abnormalities present are accounted for by roentgenographic abnormalities not related to pulmonary embolism

The panelists expressed the degree of perfusion to both lungs (the right lung was considered to receive 55 per cent of the total perfusion and the left lung 45 per cent) The perfusion defects in the anterior and posterior views were averaged to give the percentage perfusion defect for the scan set

To eliminate the problem of three angiogram readers vs. five scan readers the findings of one angiogram reader (index angiogram reader) and

Table II Diagnosis of pulmonary embolism

Angiographic panel		*Lung scan panel*					
		High probability (1 0 1 49)		*Medium probability (1 50 2 49)**		*Low probability (2 5-3 5)*	
Classification	*No of patients*	*No*	*%*	*No*	*%*	*No*	*%*
Massive embolism	99	72	72	24	24	3	3
Submassive embolism	56	26	46	21	37	[illegible]	17
No pulmonary emboli (nondiagnostic)	7	2	28	4	57	1	15
Total	162						

*Score based on
1 = high probability of pulmonary embolism
2 = medium probability of pulmonary embolism
3 = low probability of pulmonary embolism
4 = no evidence of pulmonary embolism

Note This table compares the diagnostic categorization of patients by the five members of the lung scan panel with the number of patients classified according to clot(s) size by the three angiogram panelists Each patient received a numerical score by each lung scan reader and the mean score of the five panelists was used to categorize the patients in the ranges indicated

one scan reader (index scan reader) who most frequently agreed with colleagues in their own panel were chosen for analysis

Results Reliability of diagnosis procedures

A total of 176 patients were admitted to the USPET (Urokinase-Streptokinase Pulmonary Embolism Trial) study by the investigators at the 11 participating medical centers Pulmonary perfusion scans performed at the time of entrance into the study, were available from 162 patients

Angiographic analysis A total of 107 patients were defined as having massive pulmonary emboli and 60 patients as having submassive pulmonary emboli Seventy eight per cent of the patients had bilateral emboli identified on angiogram

Eleven of 176 patients admitted to the study on the basis of a positive angiogram for pulmonary emboli by investigators at their respective medical centers failed to unanimously meet the angiogram panel s criteria for the diagnosis of pulmonary embolism In five patients none of the three panelists could identify abnormalities compatible with the diagnosis of pulmonary embolism In four patients only one of the three panel members accepted the diagnosis In seven patients two panel members reported that the diagnosis of pulmonary embolism could be made In 160 patients all three panel members agreed on the diagnosis of pulmonary embolism Thus there was panel disagreement on the diagnosis of pulmonary emboli in less than 6 per cent of the patients

Lung perfusion scan analysis Data from the lung scan panel were available on 162 patients The diagnostic consistency of the lung scan panel for the total of 162 patients scans is shown in Table I Complete agreement with respect to the diagnosis of pulmonary embolism was reached in 31 per cent of the patients In 26 per cent of the patients one of five panel members disagreed by one diagnostic category with the other panelists In 2 per cent of the patients one panel member differed by two diagnostic categories with the other panel members In 19 per cent of the patients two panel members disagreed with the other three panelists by one diagnostic category In 22 per cent of the patients there was disagreement by one or more panel members by two categories In 32 of the 112 patients in whom there was a two diagnostic category difference disagreement was by at least two panel members

There was a 3 9 per cent incidence of scans considered technically unsatisfactory by a majority of the scan panelists in the patient group where there was complete agreement on the diagnosis In those patients' lung scans where there was disagreement on the diagnosis or category placement there was an incidence of 14 3 per cent technically unsatisfactory scans In 50 patients where there was complete agreement the incidence of massive embolism was 70 per cent There was 112 patients in whom there was disagreement and the incidence of massive embolism was 49 per cent In 48 of the 50 patients in whom there was complete lung scan panel agreement

Table III Diagnosis of pulmonary emboli

Lung scan index reader		*Angiographic index reader*					
		Diagnostic evaluation			*Severity rating*		
	No of patients	*Submassive*	*Massive*	*No emboli*	*Severe*	*Moderately severe*	*Not severe*
High probability	117	29	85	3	60	44	9
Medium probability	26	14	8	4	3	11	9
Low probability	18	10	7	1	2	9	6
Nondiagnostic	1	1	0	0	0	0	1
Totals	162	54	100	8	65	64	25

Note: The table compares the diagnostic evalu tion nd severity rating by the index a giograph r with the number of patients placed in ach of the ... diagnostic categories by the ind x lung scan reader The e ght angiograms read a n nd gnostic by th inde reader were not gi en a sev rity reading.

the diagnostic evaluation was categorized as "high probability of pulmonary embolism

The diagnostic evaluation of the angiogram panel is contrasted with the patient categorization by the lung scan panel in Table II Patients with massive pulmonary emboli were more frequently categorized as high probability by scan than patients angiographically designated as submassive pulmonary emboli The diagnostic categorization by the lung scan panel of those patients with a nondiagnostic angiogram showed that all but one patient had at least a medium probability" classification by the lung scan panel More than half of those patients with angiographically defined submassive embolism had a medium low probability of the diagnosis of pulmonary emboli by the scan panel

Analysis of the distribution of lung scan classifications of the seven patients whose angiograms were nondiagnostic of pulmonary emboli revealed that two of seven were classified as having high probability of pulmonary embolism

Assessment according to diagnostic evaluation and severity rating by the index angiographer is compared with the diagnosis reported by the index lung scan reader in Table III When the index lung scan reader interpreted high probability of pulmonary embolism there was a corresponding agreement in the degree of severity and clot(s) size by the index angiographer Eighteen patients were reported by scan analysis to have low probability of emboli but more than 50 per cent of these patients had an angiographic rating of severe or moderately severe Only one of the 18 patients with a low probability of pulmonary emboli had a nondiagnostic angiogram

A comparison was made between the defects seen on angiogram and those seen on lung perfusion scan The majority of lesions were found in the lower lobes The right lung was more frequently involved than the left The two techniques were in agreement most often in patients in whom abnormalities were present in the lower lobe areas Disagreement was most common in the middle lobes

Evaluation of the extent of perfusion defects by the index lung scan reader compared with the index angiogram was performed In 43 per cent of the patients analyzed the estimate by the lung scan technique was within 10 per cent of the size of the defect demonstrated angiographically There was a tendency for the scan reader to estimate a larger defect than that reported by the angiogram reader A relationship was present between more extensive emboli as estimated by angiography and the larger perfusion defects estimated by scan

Morbidity and mortality rates The morbidity rate from angiograms was less than 1 per cent and the mortality rate was less than 0 5 per cent The one death occurred in a patient with known cardiomyopathy This patient died 3 days after the angiogram from probable tamponade resulting from myocardial perforation during the procedure

The morbidity rate associated with performance of the lung perfusion scan was less than 1 per cent and the mortality rate was zero

Death occurred in 16 patients 2 weeks after entrance into the trial Ten additional patients died within 3 months after entrance into the trial Two of the 16 patients who died in the first 2

weeks had nondiagnostic angiograms At post mortem one had emboli and one did not Two of the 10 patients who died between 2 weeks and 6 months who had nondiagnostic angiograms were autopsied, one had emboli and one did not Only one of the four patients with nondiagnostic angio grams also had a lung scan This patient s lung scan was read as medium' to low probability' and at autopsy (within 6 months) no emboli were present

Fourteen patients with angiograms diagnostic of pulmonary emboli died by 2 weeks after entrance into the trial Ten of the 14 were autopsied Nine of these patients had emboli The one patient without emboli at postmortem had massive emboli by angiogram and high probabil ity' by scan Six of the nine patients with emboli at postmortem had lung scans Four of the six patients had high' to medium probability' and two had 'low probability of emboli by scan

Eight of the 10 patients who died between 2 weeks and 6 months had diagnostic angiograms, four of the eight were autopsied All four patients had emboli at the time of death Three of these four patients had lung scans On scan one had 'high probability and two had low probability of emboli

Discussion

This study compares pulmonary perfusion scan findings with angiograms in patients selected for a therapeutic trial The angiogram was considered as the definitive basis for diagnosis There is no available means for objectively evaluating the accuracy of the angiogram except by autopsy Rigid criteria for the angiographic diagnosis were employed to ensure that patients without pulmonary emboli were not subjected to experi mental therapy The question that these data should answer is what information will the clini cian obtain from perfusion lung scans in patients who satisfied rigid angiographic criteria for pulmonary emboli?

Although it is recognized that angiography is the best available technique to objectively estab lish the presence of emboli in the pulmonary arterial vessels, it is not without error In the four patients reported to have nondiagnostic angio grams who were autopsied, two had emboli grossly visible in the pulmonary arteries The time interval between the initial angiogram and postmortem examination in four of the patients who had nondiagnostic angiograms prevents any firm conclusions about the accuracy of the inter pretation of the initial angiogram Because two of the four had recent emboli at postmortem, how ever, suspicions have been raised that angiograms interpreted by the strict criteria of this protocol may result in misdiagnosis In the one patient who was angiographically diagnosed as having massive emboli and who had no emboli at post mortem there was a sufficient time interval (one month) following thrombolytic and heparin ther apy to allow clot dissolution to occur Thus there are no inconsistencies in the observations throug hout this patient s course that allow one to conclude that the initial angiogram reading was incorrect In recent reports comparing lung perfu sion scans and angiograms[1] validation of the accuracy of angiography was not available In those reports of patient findings at postmortem examination performed in close proximity to the pulmonary angiogram the angiographic reports were 100 per cent correct[3, 6] Sufficient autopsy data on the accuracy of pulmonary angiography are lacking

Of interest is the high mortality rate in the four* of the nine patients who were reported to have nondiagnostic angiograms in contrast to the over all mortality rate in this study of 7 to 8 per cent These four patients were severely ill with decompensated cardiopulmonary function and this may in part explain the problem in diagnostic interpretation of the angiogram

Since the introduction of the lung perfusion scan its sensitivity has been universally recog nized Accurate information can be obtained of the blood flow in lung blood vessels as small as 50μ in diameter with this technique Equally well recognized is that the lung scanning technique lacks specificity[12, 13] The lung scan image is the expression of blood flow in the pulmonary vessels Anything that alters blood flow will give rise to an abnormal lung perfusion scan Therefore an abnormal lung scan is not necessarily indicative of pulmonary embolism This is exemplified by the recent report of scan abnormalities seen in 88 per cent of 59 patients without angiographic demonstration of embolism[11]

The data in the present studies indicate that interpretation of the lung scan to diagnose

*The diagnoses in these four patients were acute myocardial infarction congestive heart failure or pulmonary edema carcinoma of the lung and bacterial endocarditis

pulmonary embolism is difficult In more than two thirds of the lung scans reviewed by the expert panel, there was lack of agreement on the probability of pulmonary embolism Disturbing was the observation that all of seven patients without evidence of emboli on angiogram were reported to have a "high or medium probability of having pulmonary emboli by lung scan In all patients who were reported to have a low probability" of having emboli by scan 10 had massive and seven submassive emboli by angiography

In this report, some of the difficulty in interpretation may have resulted from poor technical scan quality The incidence of technically unsatisfactory scans was 14 3 per cent in patients where there was panel disagreement as opposed to 3 9 per cent where there was complete agreement within the scan panel The exclusive use of the rectilinear scan in this study as opposed to the camera scan may raise some question but superiority of one technique over the other with respect to pulmonary embolism has not been substantiated The combination of ventilation perfusion scanning may lessen the problem of interpretation but reports demonstrating the value of these two techniques are without angiographic diagnosis [8]

This study confirms that the size of the lung perfusion defect was frequently estimated to be greater by scan than by angiogram This is expected because of the sensitivity of the perfusion lung scan technique to changes in blood flow in vessels smaller in size than can be assessed by angiogram The agreement of the two techniques appears to be best in the lower lobes This may be true because blood flow is normally less in the upper lobes, making interpretation in those areas difficult

In general there was a greater degree of diagnostic agreement within the lung scan panel when the patients had massive as opposed to submassive emboli It also was observed that "high probability lung scans were more likely to be severe or massive on angiogram Discrepancies between the two techniques however were not statistically significantly different from the number of occasions that were complementary It should be noted that despite the sensitivity of the perfusion scan there were several instances in which a report of low probability of emboli by scan correlated with a diagnostic angiogram often showing massive emboli present

In this series 22 per cent of the patients had multiple unilateral emboli by angiogram and this was more common on the right side In this subgroup where unilateral defects were reported on angiogram 70 per cent of these patients had bilateral defects on lung scan In 30 per cent of this subgroup both scan and angiogram were in agreement that only unilateral emboli were present. In no patient was a single embolus described Previous reports have indicated unilateral emboli to be very rare In patients with pulmonary emboli unilateral lung perfusion abnormalities are rare In a series of 602 patients unilateral lung perfusion scan abnormalities were more common in bronchogenic carcinoma congenital heart disease and the hyperlucent lung syndrome than pulmonary emboli A unilateral scan abnormality does not exclude the diagnosis of pulmonary emboli

The clinician who must decide when to treat a patient for the presence of pulmonary emboli frequently relies on the lung perfusion scan and often wonders if or when angiography should be performed The data in this study support the accepted view that if all four views of a technically satisfactory lung perfusion scan are normal the diagnosis of pulmonary emboli is excluded In this situation angiography is not indicated If the lung perfusion scan is abnormal should angiography be performed? This study has shown that a lung scan interpreted as low probability may have a diagnostic angiogram If the patient is at unusual risk if he were treated with conventional anticoagulants or considered a candidate for surgical intervention (embolectomy or vena caval interruption) angiography is advised

This study suggests that the quandary resulting from an abnormal lung scan may arise not only because of the lack of specificity of the technique but also because of the substantial problem of interpreting the results of the lung perfusion scan The techniques of pulmonary angiography and lung perfusion scanning are not without error Therefore the clinician must thoughtfully combine all information about a given patient before instituting therapy for pulmonary thromboemboli

Summary

Pulmonary angiograms and pulmonary lung perfusion scans on 162 patients with pulmonary

embolism were comparatively analyzed Among the expert angiographic panel members who independently evaluated the studies there was consistent agreement on the diagnosis, size of the emboli, and severity Consistency of agreement among the expert *pulmonary lung perfusion scan* panelists was considerably less These data demonstrate that in addition to the lack of specificity of the lung perfusion scan for the diagnosis of pulmonary thromboemboli there is a considerable problem of interpretation in this patient population

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REFERENCES

1 Wagner H N Lung scanning in pulmonary embolism Bull Physiopathol Respir 6 65 1970
2 Szucs M M Brooks H L Grossman W et al Diagnostic sensitivity of laboratory findings in acute pulmonary embolism Ann Intern Med 74 161 1971
3 Dalen J E Brooks H L Johnson L W et al Pulmonary angiography in acute pulmonary embolism Indications techniques and results in 367 patients AM HEART J 81 175 1971
4 McIntyre K M and Sasahara A A Angiography scanning and hemodynamics in pulmonary embolism Critical review and correlations CRC Crit Rev Radiol Sci 3 489 1972
5 Moser K M Gennaro M T Rhodes G et al Correlation of lung photoscans with pulmonary angiography in pulmonary embolism Am J Cardiol 18 810 1966
6 Fred H L Bruden J A Gonzalez D A et al Arteriographic assessment of lung scanning in the diagnosis of pulmonary thromboembolism N Engl J Med 275 1025 1966
7 The urokinase streptokinase pulmonary embolism tria (Phase II) results J A M A 229 1606 1974
8 The urokinase streptokinase pulmonary embolism tria (Phase I) results Circulation 47(Suppl II) 1 108 19/3
9 McDonald I G Hirsh J and Hale G S Early rate of resolution of major pulmonary embolism Br Heart J 33 432 1971
10 Bookstein J J and Silver T M The angiographic differential diagnosis of acute pulmonary embolism Radiology 110 25 1974
11 Moses, D C Silver T M and Bookstein J J The complementary roles of chest radiography lung scanning and selective pulmonary angiography in the diagnosis of pulmonary embolism Circulation 49 1/9 1974
12 Winebright J W Gerdeo A M and Nelp W B Restoration of blood flow after pulmonary embolism Arch Intern Med 125 241 1970
13 Shoop J D Why do a lung scan? J A M A 229 567 1974
14 McNeil B J Holman L and Adelstein J The scintigraphic definition of pulmonary embolism J A M A 227 753 1974
15 Williams O Lyall J Vernon M and Croft D N Ventilation perfusion lung scanning for pulmonary emboli Br Med J 1 600 1974
16 Browse N L Clemenson G and Croft D N Fibrinogen detectable thrombosis in the legs and pulmonary embolism Br Med J 1 603 1974
17 Moser K M Rhodes P B and Hufnagel C C Chronic unilateral pulmonary artery thrombosis Successful thromboendarterectomy with a thirty month follow up observation N Engl J Med 272 1195 1965
18 White R I James A E and Wagner H N The significance of unilateral absence of pulmonary artery perfusion by lung scanning Am J Roentgenol 81 ;01 1971

The effect of coronary bypass surgery on exercise induced ventricular arrhythmias

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Ventricular arrhythmias at rest are a risk factor for death in patients with previous myocardial infarction in patients with coronary artery disease[2] and unselected asymptomatic populations. Such arrhythmias are commonly induced or aggravated by exercise in patients with coronary artery disease and are presumably related to myocardial ischemia Their significance in relation to risk of sudden death remains unknown.

Aortocoronary vein bypass surgery relieves angina and improves exercise capacity in majority of patients[7] while its effect on exercise induced ventricular arrhythmias, sudden death or subsequent myocardial infarction remains unknown

We report on the effect of coronary bypass surgery on exercise induced ventricular arrhythmias, and the relation of such arrhythmias to sudden death

Methods

Patient selection Patients considered for this study were male with stable angina pectoris of 3 months duration or longer who continued to be limited by chest pain despite medical therapy All underwent treadmill exercise testing cardiac catheterization and coronary and left ventricular angiography After these studies patients who were considered possible candidates for surgery (technically operable disease and ejection fraction over 20 per cent) and agreed to participate in the study were randomly assigned to either surgical or medical modes of therapy Bypass grafting was performed within 4 weeks Patients undergoing valve replacement or left ventricular aneurysmectomy in addition to coronary artery bypass were excluded

The study was approved by the Stanford University School of Medicine and the Palo Alto VA Hospital committees on the use of human subjects in research All patients gave written informed consent A total of 140 patients entered the study and as of April 1975 84 have completed the 1 year follow up (42 medical and 42 surgical patients) Seven patients died within 1 year of their initial study and are also included in this report

Medical therapy Medical therapy consisted of nitroglycerine long acting nitrates and propranolol The amounts of the above medication taken daily at entry into the study were similar in medical and surgical groups (equivalent to nitroglycerine at least once daily and propanolol 120 mg per day) At the end of 1 year the medical group required the same amount of medication for symptomatic relief whereas the amount of medication required by the surgical group had decreased (equivalent to nitroglycerine one or two times a week without propranolol) Fifty per cent of the surgical patients did not require any medication whereas all of the medical group required medication All patients were urged to abstain from smoking and keep physically active

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Table I Exercise induced ventricular arrhythmias—method of grading*

Grade	Arrhythmia
0	No arrhythmias
1	Rare VPB s† ($\leq$ 1 in 100 beats)
2	Frequent VPB s (> 1 in 100 beats)
3	Multiform VPB s
4	Couplets
5	Early VPB s (RR /QT<1)
6	Ventricular tachycardia
7	Ventricular fibrillation

*Modified from Lown and Wolf
†VPB Ventricular premature beat

Table II Characteristics of surgically and medically treated patients at entry

Characteristic	Surgical	Medical	p Value
No of patients	44	47	
Age	52± 1	52± 1	NS
Myocardial infarction	28(64%)	24(55%)	NS
Number of vessels diseased			
1	3(7%)	5(11%)	NS
2	13(29%)	11(25%)	NS
3	28(64%)	31(70%)	NS
Mean	2 6±0 1	2 6±0 1	NS
Ejection fraction	66± 3	69± 3	NS

No organized exercise training program was offered Anticoagulants were not employed Serum lipids were measured every 3 months and patients with elevation of serum cholesterol or triglycerides were offered dietary advice and drug treatment in a specialized Metabolic Clinic When indicated, patients in the surgical group were offered the treatment options used in the medically treated patients

Graded treadmill exercise Graded treadmill exercise tests, as in the protocol of Bruce and Hornsten,[8] were performed at time of entry into the study and repeated in 1 year Leads V_5 and II were recorded All tests were performed by the same team of technicians at least 2 hours post prandially under similar conditions and were continuously attended by a physician Patients were encouraged to exercise maximally to an individually determined end point of fatigue dyspnea, or angina Exercise was stopped earlier for the appearance of ventricular tachycardia (three or more consecutive beats) or an unstable gait One observer continuously monitored the oscilloscopic display of the electrocardiogram (ECG) and 20 second direct recordings were obtained during every minute of exercise and 8 minutes of recovery Blood pressure at rest and immediately after exercise was recorded by a sphygmomanometer with the patient in the standing position Heart rate, ST segment displacement and arrhythmias were measured and analyzed manually Long acting nitrates and digitalis glycosides were discontinued 1 day and 1 week, respectively, prior to each exercise test and propranolol was gradually tapered and discontinued over 3 to 4 days prior to the test Other antiarrhythmic therapy was stopped 24 hours before testing Ventricular arrhythmias were graded by a modification of the system proposed by Lown and Wolf[9] (Table I)

Coronary arteriography was performed with the percutaneous technique of Judkins[10] For this study, luminal size reduction of 50 per cent or more was considered significant and patients were classified into groups of one two , or three vessel disease (right left circumflex, and anterior descending artery) Left main coronary artery obstruction was considered as two vessel disease Left ventriculography followed the coronary studies and was performed in the right anterior oblique projection One year after entering the study, all patients had repeat left ventriculography and the surgically treated patients had selective graft angiograms

At the time of entry, patients were considered to have had an old myocardial infarction if two of the following three were present (1) clinical history (b) ECG evidence of Q waves (c) angiographic evidence of contraction abnormalities

Deaths in both groups were reviewed and those of patients dying from cardiac arrest without acute myocardial infarction, those pronounced dead on arrival to an emergency room and those dying in their sleep with postmortem examination revealing no cause of death were classified as sudden deaths These patients were compared to the rest of the patients who were alive or had died from other causes

Data analysis

Data on each patient were entered on a card file system and analyzed with the Stanford Computation Center s statistical package for social sciences (SPSS) program Duration of exercise in seconds, peak heart rate, double product (heart rate times systolic blood pressure) milli

meters of ST depression and the arrhythmia grade on entry and in 1 year for each treatment group were compared by Student s paired t test The two treatment groups on entry and in 1 year were compared by Student s unpaired t test The frequencies of arrhythmias and angina in each group, on entry and in 1 year were compared by the chi square test

Results

Important characteristics of the patients in both treatment groups at the time of entry are presented in Table II The two groups were similar in age the presence of old myocardial infarction, extent of coronary disease and ejection fraction Over 50 per cent had old myocardial infarction and 64 per cent had three vessel disease indicating the generally severe degree of disease present

Exercise induced ventricular arrhythmias Ventricular arrhythmias during treadmill testing (exercise and 8 minutes of recovery) in the surgically and medically treated patients on entry and in 1 year are presented in Table III There was no statistically significant difference in the frequency or grade of arrhythmias at 1 year compared with that on entry in either treatment group however the medical group exhibited a trend toward a decrease in the three arrhythmia categories and the surgical patients exhibited a trend toward an increase in two arrhythmia categories.

Ventricular arrhythmias in the surgically treated patients grouped by graft patency are presented in Table IV Patients with all grafts patent had a small increase in the frequency and severity of ventricular arrhythmias but this change was not statistically significant

Changes in the arrhythmia grade on entry and in 1 year in the surgically and medically treated patients are presented in Table V The majority of patients in both treatment groups had not changed their arrhythmia grade when tested in 1 year Thirty-one per cent of the surgically treated patients developed a higher grade arrhythmia whereas 17 per cent of the medically treated patients did so when tested at 1 year These changes were not statistically significant

Exercise induced ventricular tachycardia and fibrillation In the medical group no patient developed these arrhythmias on entry and one had a brief run of ventricular tachycardia at 1

Table III Exercise induced ventricular arrhythmias in the 42 surgically and 42 medically treated patients on entry and in 1 year

	All ventricular arrhythmias		*Frequent or complex ventricular arrhythmias (grade 2 or higher)*		*Arrhythmia grade*	
	Surgical (%)	*Medical (%)*	*Surgical (%)*	*Medical (%)*	*Surgical*	*Medical*
Entry	52	33	42	6	1.3±0.2	0.9±0.2
1 year	55	29	41	17	1.6±0.3	0.6±0.2
p value	NS†	NS	NS	NS	NS	NS

Mean ± SEM
†NS Not significant.

Table IV Exercise induced ventricular arrhythmias in the 42 surgically treated patients on entry and in 1 year grouped by graft patency

	All ventricular arrhythmias			*Arrhythmia grade*		
	A(%)†	*B(%)*	*C(%)*	*A*	*B*	*C*
Entry	80	50	48	2.4±0.9	1.0±0.3	1.2±0.3
1 year	60	40	59	1.6±0.8	0.9±0.4	1.8±0.4
p value	NS‡	NS	NS	NS	NS	NS

Mean ± SEM
†A = All grafts occluded (n = 5) B = some graft( ) patent (n = 10) C = all grafts patent (n = 27)
‡NS = Not significant

Table V Changes in the ventricular arrhythmia grade in 1 year in the surgically and medically treated patients

	Surgical	*Medical*	*p value*
Arrhythmia grade not changed	22 (52%)	26 (62%)	NS
Arrhythmia grade increased	13 (31%)	7 (17%)	NS
Arrhythmia grade decreased	7 (17%)	9 (21%)	NS

NS = Not significant.

year In the surgical group none had such arrhythmias on entry At 1 year two patients developed brief runs of ventricular tachycardia and one patient had ventricular fibrillation which was successfully cardioverted All three had had excellent clinical results after surgery with relief

Table VI Exercise induced ventricular arrhythmias in the medically treated patients Those dying suddenly compared to the rest of the patients

Patients	All ventricular arrhythmias (%)	Frequent or complex ventricular arrhythmias (grade 2 or higher) (%)	Arrhythmia grade*
Sudden death (N = 7)	43	43	0 9 ± 0 4
All others (N = 40)	33	28	0 8 ± 0 2
p value	N S†	N S	N S

*Mean ± S E M
†N S = Not significant

Table VII Exercise performance of 42 surgically and 42 medically treated patients on entry and in 1 year

Exercise characteristics	Surgical	Medical	p value
*Seconds of exercise**			
Entry	301 ± 23	276 ± 25	N S
1 year	379 ± 21	229 ± 14	< 0 0001
p value	< 0 006	< 0 08	
*Peak heart rate per minute**			
Entry	137 ± 3	132 ± 3	N S
1 year	149 ± 3	125 ± 3	< 0 0001
p Value	< 0 002	< 0 003	
Peak double† product			
Entry	212 ± 9	199 ± 7	N S
1 year	253 ± 10	195 ± 8	< 0 0001
p value	< 0 0001	N S	
ST depression (mm)			
Entry	1 7 ± 0 2	1 5 ± 0 2	N S
1 year	0 9 ± 0 1	1 6 ± 0 2	< 0 005
p value	< 0 001	N S	
Angina during test			
Entry	32 (76%)	35 (83%)	N S
1 year	7 (17%)	34 (81%)	0 001
p value	0 001	N S	

*Mean ± S E M
†Double product = $\frac{\text{peak heart rate} \times \text{systolic blood pressure}}{100}$

of angina and 20 to 40 per cent increase in the duration of exercise on treadmill, with decrease in ST segment depression All three had all grafts patent (five of five)

Ventricular arrhythmias and sudden death Seven medically treated patients died suddenly Ventricular arrhythmias on exercise in these patients were compared to those in 40 medically treated patients who are alive or dead of other causes (Table VI) No difference in the frequency or severity of arrhythmias was seen in these two groups In the surgically treated patients five died suddenly Two of these died prior to repeat evaluation in 1 year The third had no arrhythmias on exercise at 1 year One of the other two had multiform premature ventricular beats and the other developed ventricular fibrillation, was successfully resuscitated remained asymptomatic for over 2 years, then died during sleep The association of exercise induced ventricular arrhythmias and sudden death was not striking except in the extreme case of exercise induced ventricular fibrillation

Exercise capacity The results of treadmill test in both treatment groups at the time of entry and in 1 year are presented in Table VII At entry there was no difference between the surgical and medical group in any of the exercise characteristics studied When tested in 1 year the surgical group showed highly significant improvement over the medical group ($p < 0.005$ to < 0.0001) in the duration of exercise peak heart rate and double product (heart rate times systolic blood pressure), the degree of ischemic ST depression and the frequency of angina

Maximal exercise capacity of the medical group decreased in duration of exercise performed and maximal heart rate attained ($p < 0.08$ and < 0.003 respectively) The mean magnitude of ST depression (in millimeter) and the incidence of angina occurring during exercise were unchanged Exercise performance in the surgical group at 1 year showed statistically significant improvement in all five measured values (Table VIII)

When the surgically treated patients were grouped by graft patency (Table VIII) those with all grafts occluded showed no change, patients with some graft(s) patent had small but significant improvement and patients with all grafts patent had highly significant improvement in all characteristics

Discussion

Aortocoronary vein bypass surgery was introduced in 1967 for the treatment of coronary artery disease[11] Since then much experience has accumulated concerning the technique of surgery criteria for patient selection, and the natural history of operated patients The subject has

Table VIII Exercise performance of 42 surgically treated patients on entry and in 1 year grouped by graft patency

	Seconds of exercise			*Peak heart rate*			*Peak double product*			*ST depression*			*Angina*		
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A* (%)	*B* (%)	*C* (%)
Entry	435±81	[illegible]62±37	294±28	1[illegible]6±7	127±6	138±4	229±17	198±13	215±14	1.3±0.4	1.[illegible]±0.3	1.9±0.3	80	80	74
1 year	370±7[illegible]	351±4[illegible]	394±24	155±4	138±7	153±3	2[illegible]5±23	240±1[illegible]	[illegible]6[illegible]±16	0.9±0.4	0.8±0.[illegible]	0.9±0.2	20	10	19
P value	N.S.	<0.08	<0.004	N.S.	N.S.	<0.0001	N.S.	<0.04	<0.009	N.S.	<0.09	<0.004	N.S.	<0.0[illegible]	<0.001

A All grafts occluded (n = 5) B = some graft(s) patent (n = 10) C = all grafts patent (n = [illegible])

been extensively reviewed by Dunkman and associates.[1] Little information is available on the effect of coronary artery surgery on arrhythmias. Our study is focused on the effect of surgery on exercise induced ventricular arrhythmias and the relation of such arrhythmias to sudden death.

Ventricular arrhythmias on resting ECG or ambulatory monitoring are associated with a significantly increased risk of subsequent sudden death in patients with coronary artery disease. Patients resuscitated from out of hospital ventricular fibrillation in the absence of myocardial infarction have been shown to have a very high mortality rate (47 per cent in 2 years), the majority succumbing to sudden death, indicating the particularly grave prognosis of this severe arrhythmia.[7] The limited sampling of arrhythmias by the resting 12 lead ECG and the difficulties and costs involved in obtaining and analyzing extended ambulatory (Holter) ECGs have recently aroused interest in the exercise ECG as a method of eliciting significant arrhythmias and of selecting patients to receive antiarrhythmic therapy.[4, 11]

The prognostic significance of exercise induced ventricular arrhythmias has not been evaluated as thoroughly as that of ventricular arrhythmias detected by ambulatory monitoring. Vedin and associates,[4] in a representative population sample of 793 men, found two cases of sudden death. These patients had frequent premature ventricular beats at rest which were increased by exercise. Rodstein and associates[5] failed to find such an association in insured persons. Arrhythmias detected by ambulatory monitoring, however, correlate reasonably well with those seen on exercise testing.[6, 7] The reproducibility of exercise-induced arrhythmias is lower than that of arrhythmias detected by continuous monitoring. The validity of the exercise method of inducing ventricular arrhythmia is supported by similar data obtained from ambulatory monitoring. DeSoyza and associates[14] have reported data from Holter monitoring of patients with stable angina treated surgically and medically using a prospective randomized protocol similar to the one employed in the present study. On entry the incidence of ventricular arrhythmias was similar in both groups and at 1 year no difference was noted.

Mathur and associates commented on an increase in severity of exercise induced ventricular arrhythmias in four patients treated surgically, but no systematic study of the problem was carried out.

It has been suggested that long term treatment of patients with high grade ventricular arrhythmias detected by ambulatory monitoring or by exercise testing may decrease the risk of sudden death. In a controlled study of 78 patients recovering from myocardial infarction, procaine amide decreased the frequency of major ventricular arrhythmias detected by ambulatory monitoring without significantly decreasing the frequency of sudden death. On the other hand, patients treated with alprenolol following myocardial infarction had a significant decrease in sudden death, presumably due to an antiarrhythmic action of the drug. Further studies are necessary before any firm conclusion can be drawn on the effect of antiarrhythmic therapy which decreases the frequency of ventricular arrhythmias on sudden death.

Coronary artery bypass surgery has been advocated as an effective treatment for life threatening ventricular arrhythmias, and several case reports have demonstrated abolition of ventricular tachycardia and fibrillation after successful coronary surgery.[2, 24] Our results obtained in patients operated on for angina do not reveal any

significant change in the frequency or severity of exercise induced ventricular arrhythmias after surgery In fact, high grade ventricular arrhythmias occasionally appeared after successful surgery Patients with *all* grafts patent had the greatest improvement in exercise capacity and achieved higher heart rates with less myocardial ischemia The same subgroup of patients also showed a tendency to more frequent and higher grades of arrhythmias Thus myocardial ischemia may not be the only important factor in the production of ventricular arrhythmias during exercise The arrhythmogenic action of catecholamines at the higher levels of exercise could have contributed to the high frequency of arrhythmias In a large number of patients with coronary artery disease, absence of angina and higher heart rates during treadmill testing were associated with more frequent arrhythmias,[12] suggesting a similar mechanism

The effect of propranolol cannot be completely excluded All exercise tests were performed 24 to 48 hours after cessation of propranolol Surgical patients were taking less propranolol than medical patients and 50 per cent of the surgical patients were not taking propranolol If continuous propranolol medication has a delayed antiarrhythmic effect persisting beyond 24 to 48 hours after stopping the drug this could explain the data obtained Further studies of this problem are indicated

It may be speculated that the frequency and severity of arrhythmias in the surgical group were related to a higher heart rate and a higher amount of exercise performed at 1 year compared to the medical group, where a lower heart rate during exercise was attained The mean maximal heart rate in the surgical group at one year was 149 per minute, and 125 per minute in the medical group The design of the study did not permit evaluation of patients at the same heart rate and, despite the fact that maximal tests were performed, arrhythmias could be related to heart rate

The improvement in exercise capacity following successful coronary surgery observed in the present study is in agreement with reports of other workers [9,45]

Seven medically treated and five surgically treated patients died suddenly The difference between groups is not significant The frequency and severity of ventricular arrhythmias on exercise in these patients was not different except one patient with exercise induced ventricular fibrillation after successful surgery

Conclusions

One year following successful aortocoronary bypass surgery, the frequency and severity of exercise induced ventricular arrhythmias are not decreased despite relief of myocardial ischemia as evidenced by graft patency, substantial improvement in maximal exercise performance decrease in ST segment depression during exercise, and relief of angina

Analysis of 12 deaths in the study group did not suggest that exercise induced ventricular arrhythmias were useful predictors of sudden death except in one patient who developed ventricular fibrillation during exercise, was resuscitated, and died 2 years later during sleep

Aortocoronary bypass surgery should not be expected to decrease ventricular arrhythmias induced by exercise

Summary

Ninety one patients with angiographically proved coronary artery disease and stable angina were randomly assigned into surgical and medical therapy Graded exercise tests were performed on entry into the study and repeated in 1 year Ventricular arrhythmias during exercise and minutes of recovery were studied Arrhythmias were graded on a scale of 0 to 7 by their presumed severity On entry both groups were similar in the severity of coronary disease, exercise capacity and frequency and severity of exercise induced ventricular arrhythmias At 1 year the frequency and severity of arrhythmias remained unchanged in both groups whereas the surgically treated patients showed a marked improvement in their exercise capacity ($p < 0.005$) The medically treated patients had a slight deterioration in their work capacity which however did not achieve statistical significance ($p = 0.08$)

Twelve patients died suddenly In seven medically treated patients who died suddenly, the frequency and severity of ventricular arrhythmias on exercise were not different from those of the rest of the medical patients In the five surgically treated patients who died suddenly one had multiform premature ventricular beats a

second developed ventricular fibrillation (2 years before dying suddenly) and a third had no arrhythmias during exercise Two died before the 1 year evaluation

Successful coronary surgery improves exercise capacity without decreasing associated ventricular arrhythmias Exercise induced ventricular arrhythmias, with the exception of ventricular fibrillation may not be closely associated with the risk of sudden death

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REFERENCES

1 The Coronary Drug Project Research Group Prognostic importance of premature beats following myocardial infarction J.A.M.A. 223 1116 1973.

2. Kotler M N Tabatznik, B Mower M M., and Tominaga, S Prognostic significance of ventricular ectopic beats with respect to sudden death in the late postinfarction period, Circulation 47 959 1973

3. Chiang B N Perlman L V Ostrander L D Jr., and Epstein, F H Relationship of premature systoles to coronary heart disease and sudden death in the Tecumseh epidemiologic study Ann Intern Med 70 1159 1969

4. Hinkle, L E Jr Carver S T and Stevens M The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle aged men Am J Cardiol. 24 629 1969

5. Goldschlager N Cake D and Cohn K Exercise induced ventricular arrhythmias in patients with coronary artery disease Their relationship to angiographic findings, Am. J Cardiol, 31 434 1973

6. Blackburn H Taylor H L. Hamrell, B Buskirk E Nicholas, W C and Thorsen R D Premature ventricular complexes induced by stress testing Their frequency and response to physical conditioning Am J Cardiol 31 441 1973

7 Dunkman W B Perloff J K Kastor J A and Shelburne, J C Medical perspectives in coronary artery surgery—A caveat Ann Intern Med 81 817 1974

8. Bruce R. A and Hornsten T R Exercise stress testing in evaluation of patients with ischemic heart disease Prog. Cardiovasc. Dis 11 371 1969

9 Lown B and Wolf M Approaches to sudden death from coronary heart disease Circulation 44 130 1971

10. Judkins, M Selective coronary arteriography Part I A percutaneous transfemoral technic Radiology 89 815 1967

11 Favaloro R G Saphenous vein autograft replacement of severe segmental coronary artery occlusion Operative technique Ann Thorac Surg 5 334 1968

12. Baum R S Alvarez H and Cobb L Survival after resuscitation from out of hospital ventricular fibrillation, Circulation 50 1231 1974

13. Jelinek, M V and Lown, B Exercise stress testing for exposure of cardiac arrhythmia Prog Cardiovasc Dis 16 497 1974

14. Vedin, J A. Wilhelmsson C E Wilhelmsen L Bjure J and Ekstrom-Jodal B Relation of resting and exercise induced ectopic beats to other ischemic manifestations and to coronary risk factors Men born in 1913, Am J Cardiol. 30 25 1972

15 Rodstein, M Wolloch L. and Gubner R S Mortality study of the significance of extra systoles in an insured population Circulation 44 617 1971

16. Crawford M O Rourke R A Ramakrishna N Henning, H., and Ross, J Comparative effectiveness of exercise testing and continuous monitoring for detecting arrhythmias in patients with previous myocardial infarction Circulation 50 301 1974

17 Ryan M Lown B and Horn H Comparison of ventricular ectopic activity during 24 hour monitoring and exercise testing in patients with coronary heart disease N Engl J Med 292 224 1975

18. Faris, J V McHenry P L., Jordan J W., and Morris, S N Incidence and reproducibility of ventricular arrhythmias during maximal exercise testing in normal men Am. J Cardiol. 35 136 1975

19 Kosowsky B D., Taylor J Lown B and Ritchie R. F Long term use of procaine amide following acute myocardial infarction Circulation 47 1204 1973

20 Wilhelmsson C Wilhelmsen L., Vedin J A Tibblin G and Werkö L Reduction of sudden deaths after myocardial infarction by treatment with alprenolol Lancet 2 1157 1974

21 Bryson A L Parisi, A F Schechter E., and Wolfson S Life threatening ventricular arrhythmias induced by exercise Cessation after coronary bypass surgery Am J Cardiol. 32 995 1973

22. Nakhjavan F K Morse D P Nichols, H T., and Goldberg H Emergency aortocoronary bypass Treatment of ventricular tachycardia due to ischemic heart disease J.A.M.A 216 2138 1971

23 Hutchinson J E Kemp H G and Schwarz, M J Emergency treatment of cardiac arrest in CHD with coronary bypass graft J.A.M.A. 218 1645 1971

24 Ecker R R Mullins, C B Grammer J C Rea, W J., and Atkins, J M Control of intractable ventricular tachycardia by coronary revascularization Circulation 44 666 1971

25 Castle L. W Siegel W., Proudfit W L. and Heupler F A Ventricular fibrillation and coronary atherosclerosis with normal maximal exercise test Cleveland Clin Q 39 163 1972.

26 Cline R. E Armstrong R G., and Stanford W Successful myocardial revascularization after ventricular fibrillation induced by treadmill exercise J Thorac Cardiovasc. Surg 65 802, 1973

27 Alexander S Makar Y and Ellis, F H Recurrent ventricular fibrillation Treatment by emergency aortocoronary saphenous vein bypass J.A M A 226 70 1974

28 Nordstrom L A Lillehei, J P Adicoff A Sako Y and Gobel F L Coronary artery surgery for recurrent ventricular arrhythmias in patients with variant angina Am Heart J 89 236 1975

29 Mathur V S Guinn G A Anastassiades L C Chahine R A. Korompai, F L Montero A C and Luchi, R. J Surgical treatment for stable angina pectoris Prospective randomized study N Engl J Med 292 709 1975

30 Bartel, A. G Behar V S Peter R. L. Orgain E S and Kong Y Exercise stress testing in evaluation of aortocoronary bypass surgery Report on 123 patients Circulation 47 141 1973

31 Gurney T E., Rubenstein J J Sanders, C A. and Mundth, E D Functional evaluation of coronary

significant change in the frequency or severity of exercise induced ventricular arrhythmias after surgery In fact high grade ventricular arrhythmias occasionally appeared after successful surgery Patients with *all* grafts patent had the greatest improvement in exercise capacity and achieved higher heart rates with less myocardial ischemia The same subgroup of patients also showed a tendency to more frequent and higher grades of arrhythmias Thus, myocardial ischemia may not be the only important factor in the production of ventricular arrhythmias during exercise The arrhythmogenic action of catecholamines at the higher levels of exercise could have contributed to the high frequency of arrhythmias In a large number of patients with coronary artery disease absence of angina and higher heart rates during treadmill testing were associated with more frequent arrhythmias [12] suggesting a similar mechanism

The effect of propranolol cannot be completely excluded All exercise tests were performed 24 to 48 hours after cessation of propranolol Surgical patients were taking less propranolol than medical patients and 50 per cent of the surgical patients were not taking propranolol If continuous propranolol medication has a delayed antiarrhythmic effect persisting beyond 24 to 48 hours after stopping the drug this could explain the data obtained Further studies of this problem are indicated

It may be speculated that the frequency and severity of arrhythmias in the surgical group were related to a higher heart rate and a higher amount of exercise performed at 1 year compared to the medical group, where a lower heart rate during exercise was attained The mean maximal heart rate in the surgical group at one year was 149 per minute, and 125 per minute in the medical group The design of the study did not permit evaluation of patients at the same heart rate and despite the fact that maximal tests were performed, arrhythmias could be related to heart rate

The improvement in exercise capacity following successful coronary surgery observed in the present study is in agreement with reports of other workers [9, 43]

Seven medically treated and five surgically treated patients died suddenly The difference between groups is not significant The frequency and severity of ventricular arrhythmias on exercise in these patients was not different except in one patient with exercise induced ventricular fibrillation after successful surgery

Conclusions

One year following successful aortocoronary bypass surgery, the frequency and severity of exercise induced ventricular arrhythmias are not decreased despite relief of myocardial ischemia as evidenced by graft patency, substantial improvement in maximal exercise performance, decrease in ST segment depression during exercise, and relief of angina

Analysis of 12 deaths in the study group did not suggest that exercise induced ventricular arrhythmias were useful predictors of sudden death except in one patient who developed ventricular fibrillation during exercise, was resuscitated, and died 2 years later during sleep

Aortocoronary bypass surgery should not be expected to decrease ventricular arrhythmias induced by exercise

Summary

Ninety one patients with angiographically proved coronary artery disease and stable angina were randomly assigned into surgical and medical therapy Graded exercise tests were performed on entry into the study and repeated in 1 year Ventricular arrhythmias during exercise and 8 minutes of recovery were studied Arrhythmias were graded on a scale of 0 to 7 by their presumed severity On entry both groups were similar in the severity of coronary disease, exercise capacity, and frequency and severity of exercise induced ventricular arrhythmias At 1 year the frequency and severity of arrhythmias remained unchanged in both groups whereas the surgically treated patients showed a marked improvement in their exercise capacity ($p < 0.005$) The medically treated patients had a slight deterioration in their work capacity which, however, did not achieve statistical significance ($p = 0.08$)

Twelve patients died suddenly In seven medically treated patients who died suddenly, the frequency and severity of ventricular arrhythmias on exercise were not different from those of the rest of the medical patients In the five surgically treated patients who died suddenly one had multiform premature ventricular beats, a

Lupus cardiomyopathy Cardiac mechanics, hemodynamics, and coronary blood flow in uncomplicated systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) has emerged from the status of a medical rarity to that of a disorder with markedly rising incidence SLE is characterized by a multisystem involvement. Clinical reports have shown cardiovascular abnormalities in from 52 to 80 per cent of cases,[1 11 3 3] e g pericarditis myocarditis and endocarditis (Libman Sacks) electrocardiographic (ECG) changes heart murmurs systemic and pulmonary hypertension Recent studies in some of our patients with SLE in whom cardiac catheterization was performed revealed abnormalities of myocardial contractility and coronary hemodynamics Since there are no data available concerning cardiac mechanics as well as systemic and coronary hemodynamics in SLE this report described hemodynamic findings in a group of young patients with SLE

Methods

Studies were carried out in five female patients (mean age 35 years) during right and left heart catheterization All patients gave their informed consent for this examination They were studied in the fasting state and under local anesthesia without further premedication

Left ventricular pressures were measured through catheter tip manometers (Millar Instr) and recorded on a Honeywell UV recorder In two patients (M K S B) fluid filled catheter systems (pig tail Cordis) and microdisplacement transducers (Statham P 23 Gb) were used These catheters were connected directly to the pressure transducer The fluid filled catheter system had a natural frequency above 20 Hz and a phase lag linear with frequency in this frequency range Overshoots as well as motion artifacts were not presented and cineventriculograms did not indicate excessive catheter motion at rest nor under the influence of dipyridamole All pressures were referred to zero level 10 cm above the table top The first time derivatives of left ventricular pressures were continuously calculated by a resistance capacitance differentiating circuit (time constant 1 msec) Cardiac output was measured by thermodilution[1 3] It may be noted that cardiac index ($\overline{CI}$) was moderately increased in the normal group ($\overline{CI}$ 3 97 L /min /M[2]) (Table II) when compared to data from other reports ($\overline{CI}$ 3 52 [2] and 3 63 L /min /M[2 31]) and that cardiac index values in SLE ($\overline{CI}$ 3 13 L /min /M) although considerably lower than the normal group fall within the lower standard range This may be due to the absence of any analgesic and sedative premedication in all patients Premedication was consequently omitted in order to exclude any drug induced cardiac depressant effects e g on cardiac output and maximum rise of left ventricular pressure development which have been demonstrated e g for meperidine [1 3] and barbiturates [2]

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bypass surgery by exercise testing and oxygen consumption Circulation 47 48(Suppl III) 141 1973
32 Dodek A Kassebaum D G and Griswold H E Stress electrocardiography in the evaluation of aortocoronary bypass surgery AM HEART J 86 292 1973
33 Najmi, M Ushiyama K Blanco G Adam A, and Segal B L Results of aortocoronary artery saphenous vein bypass surgery for ischemic heart disease Am J Cardiol 33 42 1974
34 Knoebel S B McHenry P L Phillips J F and Lowe D K The effect of aortocoronary bypass grafts on myocardial blood flow reserve and treadmill exercise tolerance Circulation 50 685 1974
35 Balcon, R Honey M Rickards A F Sturridge M F Walsh W Wilkinson R D and Wright J F C Evaluation of exercise testing and atrial pacing on results of aorto coronary bypass surgery Br Heart J 36 841 1974
36 DeSoyza N Murphy M Bissett J and Kane J Personal communication

Table I Laboratory findings in SLE

	M K	H K	A S	S B	M B
Sedimentation rate	↑ ↑	↑	↑	↑ ↑	↑ ↑
Hemoglobin (below 11 Gm per 100 ml)	↓	↓	↓ –	↓	↓
Gamma globulins	↑ ↑	↑	↑ ↑	↑ ↑	↑ ↑
Immune globulins	↑(IgG)	–	↑(IgG)	↑(IgG IgM)	↑(IgG)
Rheumatoid factor	+1 80	+1 20	+1 40	+1 160	∅
LE factor†	+	+	+	–	+
Antinuclear factor‡	+ +	+ +	+ +	–	+ + +
Complement (C' C)	↓	∅	↓	∅	↓
Coombs test (direct)	+	+	∅	∅	∅

– normal ↑ increased ↓ decreased ↑– ↓– bord rline + pos tive – negati e ∅ not investigated.
†Nucleoprotein l tex test.
‡Determination by immune fluorescence at the time f heart ath t rization

Table II Right heart pressures cardiac output and derived measures

Patient	P (mm. Hg)	P (mm. Hg)	$\bar{P}$ (mm Hg)	CO (L /min)	CI (L /min / M)	HR (L /min)	SV (ml)	SVI (ml / M)
M K.	8	6	15	16	3 12	[illegible]	[illegible]	46.5
H K	8	8	14	91	3 0	68	8	9
A. S	6	[illegible]	19	5 3	91	0	6	44 6
S B	13	12	22	6 06	3 28	68	8	50.3
M B	9	10	17	6 0	3 1	80	5	43.6
x (SLE)	8.8	8 6	1 4	5 68	3 13	2 4	9	48.38
x ± SEM (N)	5.5	6.2	1	7 1	3 97	80	90	68.5
	± 0.5	± 1 2	± ?	± 0 49	± 0 3	± 2	± 6	± 8 4

P_{ra} mea right atrial press re P rv right v ntricular d di tolic pressu e P m n pulmonary artery pressure CO rdiac output CI, cardiac index HR, heart rate SV tr ke olum SVI str ke lume ind x

matographic analysis of argon in arterial and coronary venous blood Details as well as the accuracy of this method which allows measure ments of coronary blood flow up to 480 to 500 ml per minute × 100 Gm have been published previously in detail An argon oxygen mixture (79 per cent argon–21 per cent oxygen) was applied through a tightly fitting mouthpiece during a brief period of adaptation the patient breathed room air through this system Then the argon-oxygen mixture was connected abruptly At the same time the sampling of arterial (aortic catheter) and coronary venous blood (sinus coronarius catheter) was started with a special motor pump unit The sampling periods lasted 5 minutes in all patients Determination of the argon blood concentrations was performed after extraction through a specially designed extrac tion chamber[3] by gas chromatography (trace gas analyzer 1533B Varian Darmstadt/FRG) Cal culation of coronary blood flow was performed according to the formula of Kety and Schmidt

Measurements of coronary blood flow were carried out under resting conditions and under maximum coronary vasodilation The latter was achieved by the intravenous injection of a potent coronary vasodilator (dipyridamole 0 5 mg per kilogram) which was given to each patient in fractions appropriate to exert no considerable side effects on aortic pressure as well as on heart rate under the influence of dipyridamole (0 5 mg per kilogram intravenously in 12 to 15 minutes) increases in heart rate averaged 12 per minute (normal subjects) and 11 per minute (SLE patients) Mean aortic pressure decreased by [illegible] mm Hg (normal) and by 5 mm Hg (SLE) There were no detectable changes in left ventricular end diastolic pressure in either group Coronary vascular resistance (mm Hg/ml /min × 100 Gm) was determined as the ratio between mean diastolic aortic pressure ($\bar{P}_{d}$) minus mean left ventricular diastolic pressure ($\bar{P}_{LVD}$) and coronary blood flow of the left ventricle ($\dot{V}$cor) R = ($\bar{P}_{d}$ – $\bar{P}_{LVD}$)/$\dot{V}$cor Coronary vascular reserve was defined as the ratio between coronary

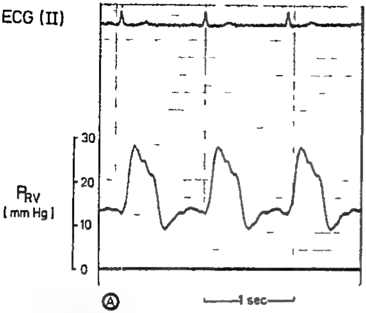

Fig 1A Representative tracing (Patient S B) from right ventricular pressure

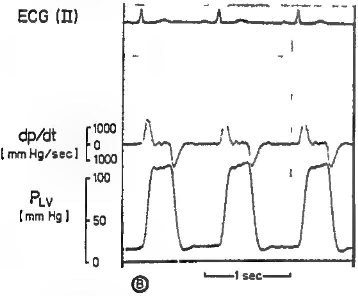

Fig 1B Representative tracing (Patient S B) from left ventricular pressure

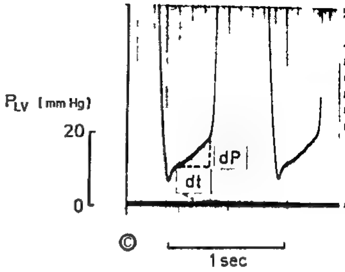

Fig 1C Representative tracings (Patient S B) from left ventricular pressure with amplified sensitivity *dP* Pressure difference from early to late diastole *dt* filling period of the left ventricle parallel to dP During *dt* left ventricle cineventriculograms were analyzed on a frame to frame basis in order to determine late diastole volume inflow parallel to dP

Single plane left ventriculograms (50 frames per second) were obtained with multiple hole catheters using power injections (Contrac) and 40 to 60 ml of 76 per cent meglumine sodium diatrizoate The single plane projections were 30° in the right anterior oblique view (RAO) Calculations of left ventricular volumes were performed by the method of Bunnell,[9] Greene,[10] and their colleagues Left ventricular wall thickness was measured on the anterior projection of the left ventricle one third of the distance from the apex Left ventricular mass was calculated according to a modification of the method of Rackley and associates [8] Ejection fraction was determined as the ratio of stroke volume and left ventricular end diastolic volume Late diastolic volume influx into the left ventricle (dV) was taken as the volume parallel to the same interval as the pressure change (dP) and it was estimated by determination of early and late diastolic left ventricular volumes on a frame to frame basis (see Fig 1) The ratio of both variables (dP/dV) that is, the relationship between simultaneously measured diastolic pressure and volume changes, was taken as an index of diastolic stiffness of the left ventricle

Isovolumic segments of systole were obtained appropriate to allow the relation between contractile element velocity (V_{CE}) and isovolumic pressure to be analyzed in its ascending and descending limb of the pressure velocity curve Maximum velocity of contractile element shortening (V_{max}) was calculated by extrapolation to zero load of the isovolumic IP to V_{CE} curve [21] For these measurements exclusively left ventricular pressure recordings with high paper speed (200 mm per second) were used The ratio (dp/dt/K × p) was calculated and related to the corresponding isovolumic pressure changes Series elastic constant was assumed as 32 per muscle length [24]

Coronary blood flow determinations were carried out subsequent to right and left heart catheterization and prior to left ventriculography by means of the argon method with gas chro

lography Mean right atrial and right ventricular end-diastolic pressure was moderately increased [illegible] SLE whereas left ventricular end diastolic pressure was considerably elevated averaging 64 per cent when compared to the normal subjects Cardiac output and cardiac index were reduced in SLE by [illegible] and [illegible] per cent respectively Stroke volume and stroke volume index were found smaller by 12 to 14 per cent Pressure derived indices of the isovolumic contraction phase (dp/dt$_{max}$ t-dp/dt dp/dt$_{m}$ /IP V$_{m}$) were altered in the direction of a decrease of myocardial contractility in SLE by 33 to 48 per cent when compared to the normal group (Tables II III and IV)

Left ventricular end diastolic volume was nearly the same in both groups In contrast left ventricular end systolic volume was increased in SLE by 15 per cent Ejection fraction was reduced by 23 per cent Left ventricular volume inflow during the late diastole (dV) was smaller in SLE by [illegible] per cent The corresponding pressure difference during late diastole (dP) showed an increase by [illegible] per cent According to the decrease of dV and the increase of dP the ratio dP/dV was considerably increased in SLE averaging 91 per cent in comparison to the normal group Diastolic pressure volume relationships revealed greater steepness in SLE and an upward shift to higher pressure values (Fig 2) This means that in comparison to the normal group an equal diastolic volume inflow into the left ventricle in SLE was associated with higher diastolic pressure rise [illegible] that diastolic volume inflow was markedly reduced at comparable diastolic filling pressure change Left ventricular wall thickness (normal 1 1 ± 0 07 cm SLE 0 98 cm) and left ventricular wall volume (normal 106 ± 12 ml SLE 104 ml) were essentially the same in both groups

Coronary hemodynamics and myocardial oxygen consumption Coronary blood flow of the left ventricle was moderately increased in SLE under resting conditions (Table V) Under maximum pharmacologically induced coronary vasodilation (dipyridamole) however coronary blood flow increased in SLE to only 159 per cent whereas in the normal group an average increase to 490 per cent was found Coronary vascular resistance was essentially normal under resting conditions However under maximum coronary vasodilation coronary vascular resistance was decreased in SLE by [illegible] per cent only whereas in the normal

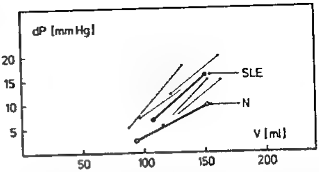

Fig 2 Left ventricular pressure-volume relationships obtained from diastolic volume changes (abscissa) and from the corresponding pressure difference *dP* (ordinate) Clear circles, mean values of the normal group (N) small black circles, pressure-volume relationships of the patients with *SLE* large black circles, mean value of the SLE group

group a decrease by 82 per cent was found Thus coronary vascular reserve that [illegible] the ratio of coronary vascular resistance under resting conditions and under maximum coronary vasodilation was strikingly reduced in SLE (SLE 1 69 normal 5 44) There were no considerable differences of left ventricular oxygen consumption in either group

Discussion

Hemodynamic findings in SLE presented in this report have demonstrated (1) increases of right and left ventricular end-diastolic pressures (2) decreases of indices of cardiac contractility (3) constancy of end diastolic volume increases of end systolic volume and decreases of the ejection fraction of the left ventricle (4) increases of left ventricular wall stiffness as indicated by increases of dP/dV (5) normal coronary blood flow under resting conditions however marked reduction of coronary vascular reserve

The increases of right and left ventricular end diastolic pressures were associated in all cases with elevations of the early diastolic dip of ventricular pressure curve (Fig 1) This increased level of diastolic pressure was independent of the choice of catheter systems since it occurred in ventricular pressure tracings with both tip manometer and fluid filled catheters In none of these patients were there cardiomegaly hypertrophy or heart failure which might help to explain the increase of end diastolic pressure in both ventricles of the patients with SLE[3, 5] However elevations of the level of diastolic pressures with or without an early diastolic dip have been noted in patients e g with pericarditis idiopathic

Table III Indexes of myocardial contractility

Patient	dp/dt_m (mm Hg/sec)†	dp/dt_m (mm Hg/sec)†	dp/dt_m (mm Hg/sec)‡	dp/dt_{mt} (mm Hg/sec)‡	$t\,dp/dt_m$ (msec)‡	dp/dt_m /IP (1/sec)‡	V_m (ML/sec)‡
M K	145	141	1 100	1 350	110	15	1.2
H K.	112	129	960	860	95	14	1 0
A S	216	430	1 700	1 760	75	23	1 6
S B	224	238	1 400	1 500	100	19	1 3
M B	160	200	1 040	1 080	90	19	1 1
$\bar{X}$(SLE)	171 4	227 6	1 240	1 310	94	18	1.24
$\bar{X}$ ±SEM (N)	—	—	1 850	1 303	61	35	1 9
			± 147	± 79	± 5	± 4	± 0 06

dp/dt maximum rate of ventricular pressure development dp/dt$_m$ maximum rate of ventricular pressure fall t dp/dt time to peak dp/dt dp/dt$_m$ /IP ratio of dp/dt$_{max}$ and the isovolumic pressure V$_m$ maximum velocity of shortening extrapolated from isovolumic IP V curve.
†Right ventricle
‡Left ventricle

Table IV Left ventricular volumes and derived measures

Patient	EDV* (ml/M)	ESV (ml/M)	EF (%)	P_{LVED} (mm Hg)	dP (mm Hg)	dV (ml)	dP/dV (mm. Hg/ml.)
M. K	79 4	38 2	52	18	13 2	43	0 31
H K.	82 2	31 9	61	15	9 8	38	0 26
A. S	74 7	32 9	57	14	6 9	40	0 17
S B	87 1	38 9	55	20	8 7	39	0.22
M B	84 9	38 5	54	15	8 1	41	0 19
$\bar{X}$ (SLE)	81 6	36 1	55 8	16 4	9 34	40 2	0 23
$\bar{X}$ ±SEM (N)	83 9	23 8	72	10	7 5	58	0 12
	± 4	± 2	± 2	± 1	± 1	± 9	±0 05

EDV end diastolic volume ESV end systolic volume EF ejection fraction P left ventricular end diastolic pressure dP late diastolic pressure rise (see Fig 1C) dV late diastolic volume inflow during dt (see Fig 1C) dP/dV ratio of late diastolic pressure and volume changes

vascular resistance in the resting state and under maximum coronary vasodilation [3, 35, 40] Myocardial oxygen consumption (ml /min × 100 Gm) was determined as the product of coronary blood flow (ml /min × 100 Gm) and the arterial coronary venous oxygen difference (vol per cent) Arterial and coronary venous oxygen saturations have been measured by CO oxymetry

Hemodynamic data have been compared with a control group (n = 20) (N) studied under equal methodological conditions This group (mean age 32 years) consisted of 12 men (mean age 30 2 years) and eight women (mean age, 33 9 years) with normal right and left ventricular function Hemodynamic data especially for cardiac index contractility indexes and coronary hemodynamics were nearly identical and independent from sex within this group Accordingly all patients (both male and female) of this control group could be compared with the female SLE patients As in SLE there was no analgesic or sedative premedication in these patients All patients (SLE and control group) received no digitalis glycosides and they had all normal sinus rhythm

Results

Clinical findings Clinical features (e g skin lesions, Raynaud s phenomenon arthritis and arthralgia) as well as laboratory signs of SLE were existent for 2½ to 7 years prior to heart catheterization (Table I) No patient had clinical signs of cardiac dysfunction except for soft and uncharacteristic systolic murmurs (M K , H K , S B) and moderate accentuations of the second heart sound (A S M B) The ECG and chest x ray films showed no arrhythmias and conduction defects nor cardiac hypertrophy and cardiomegaly Moreover, right and left heart catheterization and left ventriculography revealed no abnormal pressure gradients valve lesions septal defects or intraventricular contour abnormalities

Intracardiac catheterization and left ventricu

the increased left ventricular stiffness measured in vivo Moreover the myocardial lesions themselves, e g necrosis, atrophy and fibrous transformation, will be associated with loss of contractile mass and therefore may predominantly contribute the decreased contractile state in SLE

The marked decrease of coronary vascular reserve in SLE that is the refractoriness of the coronary vascular system to pharmacological coronary vasodilation represents a remarkable hemodynamic condition It is the consequence of a pathologically increased coronary vascular resistance in SLE According to studies in more than 300 patients with various diseases of the heart, decreases of coronary vascular reserve as in SLE may be found exclusively in elder patients with severe coronary heart disease An increased coronary vascular resistance may be caused by increases of its vascular component itself (reduced coronary dilatation because of vascular lesions) or by an increase of its myocardial component[27, 28] (influence of myocardial abnormalities on the coronary vascular bed e g by impaired ventricular relaxation increased ventricular end diastolic pressure myocardial fibrosis) or by both Coronary blood flow measurements cannot differentiate between both functional variables and calculated coronary vascular resistance represents the over all effect of its vascular and myocardial components Since there is morphological evidence for both myocardial lesions and vascular abnormalities in SLE especially for arteritic lesions in the smaller coronary arteries and arterioles both components of coronary vascular resistance may be affected and may contribute to the diminished coronary vascular reserve in SLE

In summary results demonstrate abnormalities of cardiac pump function of contractility of left ventricular wall stiffness and of coronary hemodynamics in five young women with SLE These changes may not be specific for lupus cardiomyopathy and may occur even in other nonobstructive cardiomyopathies and collagen diseases. However clinical findings were essentially normal except for uncharacteristic heart murmurs and heart sound accentuations There were no valvular pressure gradients or valvular regurgitations and heart size and ECG showed no abnormalities Thus lupus cardiomyopathy may affect the intrinsic contractile properties of the myocardium and may be existent even in young patients without clinical signs of cardiac dysfunction

Summary

Right and left heart pressures left ventricular volumes indices of contractility myocardial wall stiffness and coronary blood flow were determined in five young women with systemic lupus erythematosus (SLE) during diagnostic right and left heart catheterization Examinations revealed (1) increases of right and left ventricular end diastolic pressures (2) decreases of cardiac output stroke volume ejection fraction contractility indices diastolic left ventricular volume inflow (3) decreases of pharmacologically induced coronary vasodilation in SLE The results demonstrate impaired pump function reduced contractility increased myocardial wall stiffness and decreased coronary vascular reserve in SLE It is concluded that lupus cardiomyopathy associated with an impairment of left ventricular function may be apparent in young women with SLE who have no clinical signs of cardiac dysfunction

REFERENCES

1 Armas-Cruz, R., Harnecker J Ducach, G Jalil, J and Gonzales, F Clinical diagnosis of systemic lupus erythematodes. Am J Med. 25 409 1958.
2 Braunwald E Ross, J Jr and Sonnenblick, E H Mechanisms of contraction of the normal and failing heart Boston 1968 Little Brown & Company
3 Bretschneider H J Cott, L., Hilgert G., Probst, R., and Rau G Gaschromatographische Trennung und Analyse von Argon als Basis einer neuen Fremdgasmethode zur Durchblutungsmessung von Organen Verh. Dtsch Ges. Kreislaufforsch. 32 67 1966
4 Brigden W Bywaters, E G Lessof M M and Ross, J P The heart in systemic lupus erythematosus, Br Heart J 22 1 1960
5 Bulkley B H and Roberts W C The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy Am. J Med 58 243, 1975
6 Bunnell I Grant C and Greene D G Left ventricular function derived from the pressure-volume diagram Am J Med. 39 881 1965
7 Diamond G and Forrester J S Effect of coronary artery disease and acute myocardial infarction on left ventricular compliance in man Circulation 45 11 1972
8 Dubois E L editor Lupus erythematosus. A review of the current status of discoid and systemic lupus erythematosus and their variants New York 1966, McGraw Hill Book Company Inc
9 Field B J Baxley W H Russell, R O Hood W P Holt, J H Dowling J T., and Rackley C E Left ventricular function and hypertrophy in cardiomyopathy with depressed ejection fraction Circulation 47 1022 1973
10 Greene D G Carlisle R Grant C., and Bunnell I

Table V Coronary hemodynamics

Patient	V ml / min 100 Gm	V † ml / min 100 Gm	R mm Hg min 100 Gm / ml	R † mm Hg min 100 Gm / ml	avDO (vol %)	O_2 consumption ml / min 100 Gm	Coronary vascular (R / R†) reserve
M K	122	172	0.86	0.55	7.1	8.7	1.56
H K	61	88	1.19	0.80	11.5	7.05	1.49
A S	112	151	0.89	0.57	10.4	11.6	1.58
S B	76	6[illegible]	1.16	1.08	9.5	7.25	1.07
M B	123	313	0.81	0.29	10.3	12.7	2.[illegible]9
x̄ (SLE)	98.8	157.2	0.99	0.66	9.76	9.46	1.69
x̄ ±SEM (N)	82	402	0.98	0.18	11.8	9.68	5.44
	± 8	± 46	±0.09	±0.02	±1.2	± 1.9	

V coronary blood flow of the left ventricle R coronary vascular resistance V † R † values obtained under maximum coronary vasodilation avDO arterial coronary venous oxygen difference

myocarditis, myocardial fibrosis, or amyloid disease of the heart, and they are commonly due to decreased myocardial extension during diastole against the passive elastic resistance of abnormal myocardium or pericardium [14, 2, 45, 46]

The term (dP/dV) (termed elastance) has proved clinical value in the sense that it indicates directional changes in elastic stiffness of the ventricular wall [7, 23] This index cannot accurately quantitate stiffness, since it individually presents only one important determinant of elastic stiffness, that is, the relationship between left ventricular diastolic pressure and volume Other determinants are ventricular volume-wall mass ratio and wall stress [9] However left ventricular wall thickness, end diastolic volumes, and left ventricular mass were normal in SLE Accordingly, the stiffness constants will not have been influenced by the ventricular volume-mass ratio, since the latter can be assumed to be essentially unaffected in SLE With precautions regarding these conditions dP/dV may be considered a useful measure for the estimation of ventricular stiffness in these patients dP/dV showed considerable increases in comparison to the normal group and diastolic pressure volume relationships were steeper in SLE at comparable end diastolic volume (see Fig 2) The conclusion can therefore be made that ventricular stiffness was increased in these patients with SLE, since decreased volume change occurred for a given increment in left ventricular diastolic pressure

In all patients there was impaired contractility during isovolumic and auxotonic systole Isovolumic indices of contractility were reduced according to an impaired contractile state of the myocardium in SLE Myocardial fiber shortening was reduced since end systolic volumes were increased at normal end diastolic volumes Consequently, stroke volume and ejection fraction were decreased in SLE Since heart rate was not markedly different in both groups, the cardiac output showed decreases which were quantitatively similar to the decreases of stroke volume The question remains whether there may be morphological evidence for alterations of ventricular stiffness and contractility in SLE In the majority of autopsies on patients with SLE lesions of the myocardium endocardium and epicardium have been found [5, 8, 11, 16, 0] The myocardial lesions (lupus cardiomyopathy) are usually found in the connective tissue corresponding to a focal or generalized myocarditis apparent by fibrinoid deposits cellular infiltrates and, in the healed stage, with increase in interstitial connective tissue and perivascular myocardial scars In many cases these myocardial lesions are associated with focal necrosis and atrophy of myocardial fiber mass The endocardium and pericardium has been found to be affected in about two thirds of patients, in the acute stage there are fibrinoid deposits whereas thickened, edematous, and fibrous tissue may occur in the healed stage It is of further interest that vascular lesions are commonly found in the small arteries and arterioles of various organs in most cases there is focal fibrinoid deposition in the wall of the vessel Fibroplastic proliferation often occurs and is associated with narrowing of the lumen of the vessel Sometimes destructions of muscular and elastic elements associated with necrosis occur Thus autopsy findings demonstrate myocardial structure abnormalities in SLE which most probably may be a responsible morphological correlate for

Non bacterial thrombotic endocarditis

CLINICOPATHOLOGIC CORRELATIONS

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Nonbacterial thrombotic endocarditis (NBTE) is no longer considered merely a postmortem pathologic curiosity. Recent emphasis has been affixed to the significant morbidity and mortality rates associated with this entity, mainly as a result of major arterial embolization from a cardiac valve thrombus. Premortem clinical recognition has been stressed.

NBTE has been associated with a spectrum of underlying diseases. However, it is seen most commonly in patients with malignant neoplasms, particularly adenocarcinomas.

McKay first associated NBTE with disseminated intravascular coagulation (DIC). Infrequent cases of NBTE occurring in patients with DIC have since been reported, but this relationship has received little emphasis.

A retrospective clinicopathologic analysis was undertaken for all cases of NBTE diagnosed at autopsy over a 10 year period at the Mount Sinai Hospital, New York City. Attention was focused upon (1) the distribution and clinical significance of peripheral organ thrombosis and infarction, (2) the diseases underlying NBTE, and (3) abnormal bleeding parameters present and the relationship of NBTE with DIC.

Materials and methods

The autopsy files of the Mount Sinai Hospital for the 10 year period 1965 to 1974 were examined to identify cases of NBTE. NBTE is the presence of a bland fibrin platelet thrombus upon a cardiac valve. Valve destruction or the presence of microorganisms within the thrombus indicated a diagnosis of infectious rather than nonbacterial thrombotic endocarditis.

The postmortem diagnosis of NBTE was made in 102 cases. In 65 the diagnosis was confirmed upon review and both pathologic material and clinical information were available for study.

The histologic slides and the autopsy reports of all 65 cases were reviewed. Clinical information was derived from both the hospital records and the clinical summary that forms a part of the postmortem record.

Fibrin degradation products (FDP) were determined qualitatively by double gel diffusion with antifibrinogen serum. Fibrinogen levels were determined by heat precipitation.

Results

Incidence. During the 10 year period of study 4096 adult autopsies were performed in this institution. The incidence of NBTE in adult deaths is at least 1.6 per cent.

Age and sex distribution. Of 65 patients with NBTE, 36 were men and 29 were women, ranging in age from 21 to 86 years. 50 patients were 50 years of age or older.

Body habitus. Of 49 patients in whom adequate description about nutritional state was available, 29 were cachectic or showed significant weight loss just prior to death. Eight patients were obese, nine were well nourished, one showed Cushingoid features, and two others were thin.

Primary diseases associated with NBTE. There were 51 patients with one or more malignant

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Estimation of left ventricular volume by one plane cineangiography Circulation 35 61 1967
11 Gross L Cardiac lesions in Libman Sacks disease with considerations of its relationships to acute diffuse lupus erythematosus Am J Pathol 16 375 1940
12 Altman P L editor Handbook of circulation Philadelphia 1959 W B Saunders Company pp 72 74
13 Harvey A M Shulman L E Tumulty A Conley C L and Schoenrich F H Systemic lupus erythematosus Review of literature and clinical analysis of 138 cases Medicine 33 291 1954
14 Hetzel P S Wood E H and Burchell H B Pressure pulses in the right side of the heart in a case of idiopathic heart failure simulating constrictive pericarditis Proc Staff Meet Mayo Clin 28 107 1953
15 Jessar R A Lamont Harvers R W and Ragan C Natural history of lupus erythematosus disseminatus Ann Intern Med 38 717 1953
16 Klemperer P Pollack A D and Baehr G Pathology of disseminated lupus erythematosus Arch Pathol 32 569 1941
17 Kety S S and Schmidt C F The nitrous oxide method for the quantitative determination of cerebral blood flow in man Theory procedure and normal values J Clin Invest 27 476 1948
18 Kochsiek K Kleinsorg H and Schütz R M Technik und Anwendung der Kälteverdünnungsmethode zur Diagnostik von Herzfehlern Klin Wochenschr 40 415 1962
19 *Kochsiek K Cott L Tauchert M Neubaur J and* Larbig D Measurement of coronary blood flow in various hemodynamic conditions using the argon technique *in* Kaltenbach M and Lichtlen P editors Coronary heart disease Stuttgart 1971 Georg Thieme Verlag p 137
20 Libman E and Sacks A A hitherto undescribed form of valvular and mural endocarditis Arch Intern Med 33 701 1924
21 Mason D T Spann J F and Zelis R Quantification of the contractile state of the intact human heart Am J Cardiol 26 248 1970
22 McKusick V A Chronic constrictive pericarditis 1 Some clinical and laboratory observations Bull Johns Hopkins Hosp 90 3 1952
23 *Mirsky J Cohn P F Levine J A Gorlin R Herman* M V Kreulen T H and Sonnenblick E H Assessment of left ventricular stiffness in primary myocardial disease and coronary artery disease Circulation 50 128 1974
24 Parmley W W Spann J F Taylor R R Sonnenblick E H and Braunwald E The series elasticity of cardiac muscle in hyperthyroidism ventricular hypertrophy and heart failure Proc Soc Exp Biol Med 127 606 1968
25 Rackley C E Hood W P Rolett E L and Young D T Left ventricular end diastolic pressure in chronic heart disease Am J Med 48 310 1970
26 Rackley C E Dodge H T Coble Y D and Hay R E Method for determining left ventricular mass in man Circulation *29 666 1964*
27 Raff W K Kosche F and Lochner W Extravasale Komponente des Koronarwiderstandes und Coronardurchblutung bei steigendem enddiastolischen Druck Pflugers Arch 327 225 1971
28 Raff W K Kosche F and Lochner W Extravascular coronary resistance and its relation to microcirculation Am J Cardiol 29 598 1972
29 Rau G Messung der Koronardurchblutung mit der Argon Fremdgasmethode Arch Kreislaufforsch 58 3?? 1969
30 Rees H A MacDonald H R Muir A L Lawrie D Burton J L and Donald K W Circulatory effects of pethidine in patients with acute myocardial infarction Lancet 2 863 1967
31 Reeves J T Grover R F Filley G F, and Blount, S G Cardiac output in normal resting man J Appl Physiol 16 276 1961
32 Schenk H Strauer B E Heiss H W and Kochsiek, K Koronarreserve und myokardialer Sauerstoffverbrauch bei Patienten mit stenosierender Koronarsklerose Verh Dtsch Ges Inn Med 79 1139 1973
33 Shearn M A The heart in systemic lupus erythematosus Am Heart J *56 452 1959*
34 Spieckermann P G and Bretschneider H J Vereinfachte quantitative Auswertung von Indikationsverdunnungsmethoden Arch Kreislaufforsch 55 211 1968
35 Strauer B E Tauchert M Heiss H W Kochsiek, K and Bretschneider H J Relation between coronary blood flow oxygen consumption and cardiac work in patients with and without angina pectoris *in* Maseri A editor Myocardial blood flow in man Methods and significance in coronary disease Torino 1972 Minerva Medica
36 Strauer B E Dynamik Koronardurchblutung und Sauerstoffverbrauch des normalen und kranken Herzens, Basel 1975 S Karger AG
37 Strauer B E Die Wirkung von Pethidin auf Herzmechanik *und Kontraktilitat des menschlichen Herzens,* Klin Wochenschr 51 1105 1973
38 Strauer B E Contractile responses to morphine piritramide meperidine and fentanyl A comparative study of effects on the isolated ventricular myocardium Anesthesiology 37 304 1972
39 Tauchert M Heiss H W Probst R and Bretschneider H J Extraktionskammer mit Dosierhahn für die gaschromatographische Bestimmung des Gasgehaltes von Blut und wässrigen Lösungen Z Kreislaufforsch 60 836 1971
40 Tauchert M Koronarreserve und myokardialer Sauerstoffverbrauch des menschlichen Herzens Basic Res. Cardiol 68 183 1973
41 Tauchert M Heiss H W Strauer B E Cott L and *Kochsiek K Der Einfluss von Vorhofflimmern auf die* Koronarreserve bei Patienten mit Mitralvitien Klin Wochenschr 49 559 1971
42 Tauchert M Kochsiek K Heiss H W Strauer B E Kettler D Reploh H D Rau G and Bretschneider H J Measurement of coronary blood flow in man by the argon method *in* Maseri A editor Myocardial blood flow in man Methods and significance in coronary disease Torino 1972 Minerva Medica
43 Tauchert M Kochsiek K Heiss H W Rau G and Bretschneider H J Technik der Organdurchblutungsmessung mit der Argon Methode Z Kreislaufforsch 60 871 1971
44 Warner H R and Wood E H Simplified calculations of cardiac output from dye dilution curves recorded by oximeter J Appl. Physiol 5 111 1952
45 Wilson R J Hoseth W Sadoff C and Dempsey M E Pathologic physiologic and diagnostic significance of the pressure pulse tracings in the heart in patients with constrictive pericarditis and pericardial effusion Am Heart J 48 671 1954
46 Zimmerman H A Intravascular catheterization Springfield Ill 1972 Charles C Thomas Publisher

Table V Clinicopathologic correlations of patients with NBTE and myocardial infarction

Age Sex	Primary disease	Symptomatology	Location of NBTE	Location of MI	Vessels occluded
61/M	Urinary bladder carcinoma	ECG diagnosis myocardial infarction aortic ejection murmur ↑ LDH ↑ SGOT	Aortic valve	Posterior wall 3 cm. in diameter	Branches of left circumflex, 2.5 cm long thrombus
29 M	Hodgkin s disease	Systolic murmur at left sternal border thrombocytopenia with bleeding septic shock with acute renal failure	Mitral valve	Apex up to 1.5 cm in diameter	Intramyocardial
59/M	Pancreatic and renal cell carcinoma (occult)	Clinical diagnosis of NBTE predominantly neurologic bowel infarction with surgical resection	Aortic and mitral valves	No gross description	Intramyocardial
49/M	Carcinoma of breast	Systolic murmur ↑ CVP congestive heart failure convulsions	Aortic and mitral valves	Posterolateral wall near apex	Intramyocardial
54/F	Adenocarcinoma of gallbladder	ECG diagnosis myocardial infarction ↑ SGOT alkaline phosphatase predominantly neurologic	Tricuspid mitral and pulmonic valves	Anterolateral	Intramyocardial

pulmonic or aortic valves There was no patient with quadrivalvular lesions

Distribution and size of vegetations Most vegetations were located on the closure margin of the valves In 10 cases however the vegetations were situated on the free edge (Table III) Vegetations were found on the nodule of Arantius in 5 patients and on the ventricular surface of aortic (2) tricuspid (1) and pulmonic valves (1)

Of 38 patients in which there was adequate measurement of size of vegetations 31 were less than 5 mm in diameter and 7 ranged in size from 5 to 10 mm There was no vegetation larger than 10 mm. Data relating to the number of vegetations were available in 54 patients Of these 38 had multiple vegetations and 12 (22 per cent) single vegetations Four patients had two isolated vegetations The size and the number of vegetations could not be correlated with the frequency or severity of thrombosis in peripheral locations

Associated valvular disease In most instances (53 patients) NBTE was found on grossly normal heart valves It was associated with probable chronic rheumatic valvulitis in 8 patients (mitral 7 aortic 1) The valvular damage was slight in more than half of these NBTE was superimposed on atherosclerotic mitral valves in 2 patients In 2 others it was noted on prosthetic aortic valves In both these patients the valvular vegetations were indistinguishable from NBTE in other cases and occurred 6 months after the valve replacement

Cardiac murmur Murmurs were heard in 31 patients during the course of their illness However in only 8 patients did the murmur exhibit a probable relationship to NBTE In 1 case the murmur increased in intensity during hospitalization and led to a premortem diagnosis of NBTE

Arterial thrombosis Table IV shows the autopsy distribution of arterial thrombi with and without associated organ infarction Infarcts usually of recent origin were most frequently found within the spleen and kidney Microthrombi were commonly noted within the adrenal liver and pancreas but related ischemic necrosis was uncommon in these organs

Intramyocardial arterial thrombosis was noted in 21 patients in 5 the vascular occlusion was

Table I Sites of primary neoplasm in NBTE

	No *
Adenocarcinoma of pancreas	12
Adenocarcinoma of colon	7
Adenocarcinoma of lung	5
Anaplastic carcinoma of lung	2
Malignant melanoma	5
Adenocarcinoma of prostate	5
Adenocarcinoma of breast	5
Adenocarcinoma of gall bladder	3
Adenocarcinoma of unknown primary site	3
Multiple myeloma	3

Two patients each with transitional cell carcinoma of urinary bladder Hodgkin s disease One patient each with gastric adenocarcinoma hepatoma hypernephroma transitional cell carcinoma of kidney acute myelogenous leukemia squamous cell carcinoma of esophagus malignant fibrous xanthoma

Table II Frequency of NBTE

Neoplasm	No of cases	Frequency (%)
Adenocarcinoma of pancreas	74	16 2
Multiple Myeloma	41	7 3
Adenocarcinoma of prostate	57	7 0
Adenocarcinoma of lung	112	4 5
Hodgkin s disease	52	3 9
Adenocarcinoma of colon	139	3 6
Adenocarcinoma of breast	139	2 8
Anaplastic carcinoma of lung	70	2 8
Adenocarcinoma of stomach	70	1 4
Leukemia	258	0 4
Reticulum cell sarcoma	63	0 0
Lymphosarcoma	53	0 0
Adenocarcinoma of ovary	46	0 0
Glioblastoma	43	0 0
Squamous carcinoma of lung	40	0 0

neoplasms at autopsy In 10 patients two malignancies were present Table I details the site and histologic type of the associated neoplasm The frequency with which NBTE is associated with these tumors at autopsy is listed (Table II) Incidence was determined only for those tumors occurring in 40 or more autopsies The great majority of associated neoplasms were adenocarcinomas Pancreatic adenocarcinoma showed the highest incidence (16 2 per cent), which was four times that of pulmonary adenocarcinoma Squamous cell carcinoma of any site, leukemia non Hodgkin lymphoma, and sarcoma were rarely associated with NBTE

In 14 patients, no neoplasm was demonstrated Four had systemic lupus erythematosus (SLE)

Table III Location of vegetations in NBTE

Location	Mitral	Aortic	Tricuspid	Pulmonary
Closure margin	17	10	1	–
Free margin	5	5	–	–
Nodule of Arantius	–	5	–	–
Ventricular surface	–	2	1	1

As described in autopsy protocol May refer to free or closure marg or elsewhere on the valve leaflet

Table IV Incidence of thrombi and infarction i patients with NBTE

Organ	Thrombi without infarction	Thrombi with infraction
Spleen	5	22
Kidney	4	22
Heart	16	5
Liver	7	3
Adrenal	11	1
Pancreas	8	1
Thyroid	6	–
Esophagus	4	–
Lung (bronchial artery)	3	–
Breast	2	–
Colon	2	–
Stomach	2	–
Skin	2	–
Prostate	2	–
Lymph node	1	2
Bladder	2	–
Vagina	1	–

The gross and microscopic appearances of NBTE in these cases fulfilled the criteria for NBTE, the specific subvalvular mitral and tricuspid lesions of Libman Sachs endocarditis were absent The remaining patients had the following diagnoses postcardiac valvular replacement (2), cirrhosis (2) one patient each with volvulus gas gangrene coronary artery-saphenous vein bypass, interstitial pneumonia perforated duodenal ulcer, and chronic renal failure

Location of NBTE The mitral valve was involved in 25 patients (38 per cent) and the aortic in 20 (31 per cent) In three and one patients, respectively, the lesion was located on the tricuspid and pulmonic valves Bivalvular involvement was noted in 15 patients—aortic and mitral (12) mitral and tricuspid (2) aortic and tricuspid (1) Two patients showed trivalvular lesions involving the tricuspid, mitral and

Table VIII Clinical pathological and laboratory findings in patients with NBTE and DIC*

Age/sex	Primary disease	Laboratory data						Microthrombi with or without infarction	Sites of bleeding
		P/T	*PTT*	*Platelets ×1 000*	*Fibrinogen*	*FDP*	*Venous thrombi*		
68 F	Carcinoma of pancreas	14 6/11 6	–	46	100	–	Splenic portal	M K E B	Brain
4 F	SLE	13 6/13 8	67 4/56 2	0	38	–	0	M K S L A B T GIT	H K Lu GIT skin
42 F	Carcinoma of pancreas	–	–	32	50-100	–	Iliac splenic	M K S	0
61/M	Carcinoma of bladder	1? 0/12 5	–	100	150	–	0	M K S L	GIT subdural
70 M	Carcinoma of colon	17 0/11 0	78 0/51 0	–	<50	–	0	M S	Hemoptysis
60 M	Carcinoma of pancreas	13 4/11 8	62 0/50 0	63	50	+	Femoral, iliac splenic	M K S L, T	0
86 F	Carcinoma of pancreas	19 0/13 0	91 0/49 0	33	–	+	Hepatic	K	Uterine
63 F	Acute myelogenous leukemia	14 0/12 0	50 2/54 0	18	155	–	0	K	GIT skin S Lu
71/M	Perforated duodenal ulcer	19 0/12 0	14 0/38 0	8?	N	–	0	M K S LN	GIT
54 F	Gastric carcinoma	–	–	90	150	–	Iliac inferior vena cava	S	0
63/M	SLE	15 0/1? 4	2 0/54 0	30	565	–	0	M K S T L, skin brain	0
64/F	Intestinal obstruction with peritonitis	17 0/14 0	100 0/30 0	70	2 5	–	0	A T	GIT

*T Testis/epididymis M myocardium K kidney E esophagus B breast LN lymph node GIT gastrointestinal tract Lu lungs S spleen L liver A adrenal, T thyroid 0 absent N normal – not determined.

dotoxin (through activation of factor XII)

Twelve patients (18 5 per cent) fulfilled the criteria for the diagnosis of DIC thus emphasizing the probable importance of this pathway in the pathogenesis of at least some cases of NBTE Associated thrombotic and hemorrhagic phenomena were present in all 12 patients The association between DIC and NBTE first noted by McKay * is known but has not been documented frequently NBTE is seen in a minority of patients with proved DIC In 22 patients with DIC studied by Robboy and associates only two had NBTE NBTE was present in two of 67 patients with DIC and malignancy studied by Goodnight The converse relationship that is the frequency of abnormal clotting in cases of NBTE is incompletely investigated It has been suggested that DIC associated NBTE probably results from thrombosis occurring in the turbulence along the line of valve closure We believe that NBTE may be an integral part of DIC similar to thrombosis within small vessels of various organs and probably occurs more than is realized

It is well known that NBTE occurs more commonly on damaged valves but may also occur on relatively normal valves Such damage includes chronic rheumatic valvulitis or nonspecific abnormalities like fibrous thickenings or fibrous and hyaline nodularities of heart valves Thus Angrist Oka and Nakoa observed that fresh vegetations were often located on an acellular fibrotic valve surface In the present study underlying valvular lesions could be identified in only 12 patients In the majority of cases NBTE was found on grossly normal valves

Vascular insufficiency with ischemic necrosis of peripheral organs is a significant factor in the morbidity and death of patients with NBTE It is probable that in these cases of DIC associated NBTE the arterial thromboses might represent in situ thrombosis rather than embolization from a valve vegetation

Table VI Neuropathology findings in NBTE

Positive	19	
Infarction		
Recent or acute		11
Old		7
Thrombosis		2
Hemorrhage		3
Negative	17	

Table VII Incidence of venous thrombi in patients with NBTE (30 patients)

Vein	*No of cases*
Iliac	7
Mesenteric	5
Femoral	5
Inferior vena cava	5
Splenic	4
Portal	4
Ovarian	3
Prostatic	3
Subclavian	2
Renal	2
Coronary	2
Hepatic	2
Jugular	1
Pulmonary	1
Pancreatic	1
Skin	1

severe enough to cause myocardial infarction Patients in whom infarction was due to athero sclerotic vascular disease were excluded The clinical and pathologic findings in these five patients are tabulated in Table V

Nineteen of 36 brains examined showed recent or old infarction hemorrhage or arterial throm bosis (Table VI) All lesions possibly related to arteriosclerotic cerebrovascular disease were ex cluded Neurologic findings were noted in 18 patients, these included focal or segmental motor deficits, convulsions, and obtundation

Major vessel thrombosis was clinically noted in the femoral (2 patients), and in the superior mesenteric artery (1 patient)

Thromboembolism within the pulmonary ar teries was a frequent occurrence, noted at autopsy in 37 cases In 6 patients, the diagnosis of pulmonary thromboembolism was suspected clinically

Venous thrombosis Nine patients had clinical lower extremity thrombophlebitis In 30 cases, there was gross autopsy evidence of venous thrombosis Table VII details the location of venous thrombosis The iliac vein was most frequently involved, followed by the femoral vein mesenteric veins, and inferior vena cava Venous thrombosis was commonly associated with malig nant neoplasms and/or disseminated intravas cular coagulation

Hemorrhage Hemorrhage was a significant postmortem finding, it occurred in 25 cases Sites of hemorrhage included the lungs (13 cases), spleen (10), gastrointestinal tract (8), skin (4), renal pelvis (3) urinary bladder (2) endometrium (2) ovary (2)

Disseminated intravascular coagulation (DIC) Twelve patients (18 5 per cent) with NBTE mani fested laboratory and occasionally clinical evi dence of DIC (Table VIII) A diagnosis of DIC was based on the presence of hypofibrinogenemia, significant prolongation of the prothrombin time and partial thromboplastin time thrombocytope nia, and demonstration of fibrin/fibrinogen degradation products Six of these patients showed venous thrombosis in various organs and in 9 patients clinical or pathologic evidence of bleeding was found Malignant neoplasia consti tuted the commonest underlying disease (8 patients) SLE was present in 2 others Ante mortem diagnosis of NBTE was suggested in 3 of these patients

Comment

In the present study, underlying malignant neoplasm was present in the great majority of cases It has been postulated that NBTE occur ring in association with malignant neoplasms might be related to a hypercoagulable state [5, 11, 14, 16] Many coagulation abnormalities have been found in patients with malignant neoplasms including hypofibrinogenemia [17, 18] hy perfibrinogenemia [19] thrombocytopenia, de creased levels of factors V VIII, and XIII,[11] and impairment of platelet function by circulating fibrin degradation products [21] It has been suggested that the probable cause of intravas cular coagulation is the presence of clot promoting substance derived from neoplastic cells Less studied, however is the mechanism of DIC in nonneoplastic conditions The mech anisms postulated for the induction of DIC in those cases include bacterial capsular antigens (through antigen antibody complexes) [2] and en

disseminated intravascular coagulation (DIC) Analysis of 26 cases, Human Pathol. 3 327 1972.
13. Horwitz, C and Ward P Disseminated intravascular coagulation, non bacterial thrombotic endocarditis and adult pulmonary hyaline membranes—An inter related triad, Am. J Med. [redacted] 272, 1971
14. Amundsen, M A., Spittel, J A., Thompson J H., and Glover C. A. Hypercoagulability associated with malig nant disease and with the postoperative state Ann. Intern. Med. 58 608, 1963.
15. Hoofer W [redacted] Hypercoagulability and verrucous endocarditis associated with *adenocarcinoma of the lung* Ann. Thorac. Surg 6 181 1968.
16. Bryan, C. S Non bacterial thrombotic endocarditis with malignant tumors, Am J Med. 46 787 1969
17. Rappaport, [redacted] I and Chapman, C G Coexistent hyper coagulability and acute hypofibrinogenemia in a patient with prostatic carcinoma, Am. J Med. 27 144 1959
18. Rosenthal, R. L. Acute promyelocytic leukemia associated with hypofibrinogenemia, Blood [redacted] 495 1963.
19. Sun, N [redacted] J Boare E J W Kazmier F J., Elveback, L R., and Owen C A. Blood coagulation studies in patients with cancer *Mayo Clin. Proc. 49 636, 1974*
20. Hagedorn, A. B Bowie, E. J W., Elveback, L. R., and Owen, C. A. Coagulation abnormalities in patients with inoperable lung cancer Mayo Clin Proc 49 647 19 4
21. Mustard J F., and Parkham, M A Factors influencing platelet function Adhesion release and aggregation, Pharmacol Rev 22 97 1970
22. Rytel [redacted] W., Dee T H Ferstenfeld J E., and Hensley [redacted] T Possible pathogenetic role of capsular antigens in fulminant pneumococcal disease with disseminated intravascular coagulation (DIC) Am J Med. *57 889* 1974
23. Abildgard [redacted] E Recognition and treatment of intravascular coagulation J Pediatr 74 163, 1969
24. McKay [redacted] [redacted] Disseminated intravascular coagulation New York 1965 *Hoeber Medical Division Harper & Row* Publishers.
25. Amromin [redacted] D and Wang S K. Degenerative verrucal endocardiosis and myocardial infarction Report of 2 cases associated with mucus producing adenocarcinoma, Br J Dis. Chest. 65 98 1971
26. McDonald R. A., and Robbins, S L. The significance of non bacterial thrombotic endocarditis An autopsy and clinical study of 78 cases, Ann Intern Med 46 255 1957
27. McDonald R. A. A study of 356 carcinoids of the *gastrointestinal tract, Am J Med. 21 867 1956*
28. Angrist, A., Oka M., and Nakoa, K. Vegetative endocarditis, Pathol. Ann. 2 155 1967

Cardiac dysfunction resulting from vascular thrombosis in association with NBTE has not been stressed by previous authors However, the association of NBTE with myocardial infarcts is not rare [3, 25] The histologic appearance is one of intramyocardial arterial thromboses with multiple infarcts This relationship should be accepted only in the presence of extensive occlusion of coronary arteries or their branches and in the absence of significant coronary atherosclerosis In this study, five patients fulfilled these criteria Antemortem diagnosis based on ECG physical findings and serum enzyme activity, was made in one case and suggested in two others The diagnosis was masked in the remainder by neurologic symptoms All the patients had underlying malignant neoplasms Myocardial infarction was the probable cause of death in three patients

Cerebral vascular thrombosis is one of the major causes of morbidity and death in NBTE [6] Baron observed cerebral embolism due to NBTE in 38 of 3,054 autopsies [9] A high index of suspicion is needed for the diagnosis to be made Guinn and associates[3] described seven out of 11 patients with stroke due to NBTE Two of four patients in whom brain scan was performed had evidence of vascular occlusion Angiography demonstrated multiple small vessel occlusion in two other patients Twenty one of 75 patients reviewed by Rosen and Armstrong[4] died as a direct consequence of cerebral lesions, 14 of which were cerebral infarcts resulting from embolism in NBTE In half of these patients the diagnosis was suspected clinically, and no patient recovered from an episode of cerebral infarction This study confirmed the significance of cerebral vascular disease related to NBTE Almost half the brains examined showed infarction or hemorrhage Thrombosis, however, was rarely demonstrated Symptomatology ranged from focal seizures to generalized convulsions and deterioration of mental function

Three criteria have been suggested for the diagnosis of NBTE presence of heart murmurs presence of an underlying disease process known to predispose to NBTE and evidence of multiple embolization to the brain, spleen, kidneys and heart [3, 5]

The presence of DIC seems to contribute significantly to NBTE and the latter should be investigated in suspected patients Although most commonly involved, little attention has been paid to the clinical manifestations of embolization and infarction in the kidney and spleen Involvement of these organs is probably a cause of high morbidity but unlikely significant death By contrast, cerebral and myocardial embolism are known causes of death in NBTE and attempts should be made to diagnose these conditions

Summary

Sixty five cases of nonbacterial thrombotic endocarditis (NBTE) were discovered at autopsy during a 10 year period—an incidence of 1 6 per cent in the adult autopsy population In 51 cases one or more malignant neoplasms were associated, adenocarcinoma represented the most frequent histologic type of related neoplasm

Coagulation abnormalities suggestive of disseminated intravascular coagulation (DIC) were present in 18 5 per cent of the cases It is possible that both the valvular and peripheral intravascular thromboses in at least some cases of NBTE represent the abnormal coagulation of DIC

Arterial thrombosis with infarction occurred in many peripheral organs Splenic and renal were most frequent, but cerebral and cardiac consequences were the most significant

REFERENCES

1 Rohner R F Prior J T and Sipple J H Mucinous malignancies venous thrombosis and terminal endocarditis with emboli Cancer 19 1805 1966
2 Barry W and Scarpelli D Nonbacterial thrombotic endocarditis Arch Intern Med 109 151 1962
3 Guinn G A., Ayala, A and Liddicoat J Clinical and therapeutic considerations in nonbacterial thrombotic endocarditis Chest 64 [illegible] 1974
4 Rosen P and Armstrong D Nonbacterial thrombotic endocarditis in patients with malignant neoplastic disease Am J Med 54 23 1973
5 Wooley C F Baba N and Ryan J M Nonbacterial thrombotic endocarditis Clinical recognition Arch Intern Med 125 126 1970
6 Remillard G M and Carpenter S Cerebral embolism due to non bacterial thrombotic endocarditis Can Med Assoc J 106 573 1972
7 Gross L and Friedberg C K Nonbacterial thrombotic endocarditis Classification and general description Arch Intern Med 58 620 1936
8 Waller B F Knapp W S and Edwards J E Marantic valvular vegetations Circulation 48 644 1973
9 Chaudhauri M R Non bacterial thrombotic endocarditis in association with mucus secreting adenocarcinomas Br J Chest Dis 65 98 1971
10 McKay D and Wahle G H Jr Disseminated thrombosis in colon cancer Cancer 8 970 1955
11 Goodnight S H Bleeding and intravascular clotting in malignancy A review Ann N Y Acad Sci 230 271 1974
[illegible] Robboy S Colman R and Minna J Pathology of

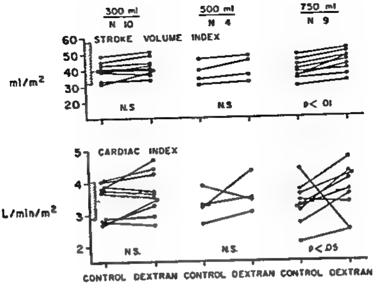

Fig 2 Effect of dextran infusion on stroke volume index and cardiac index

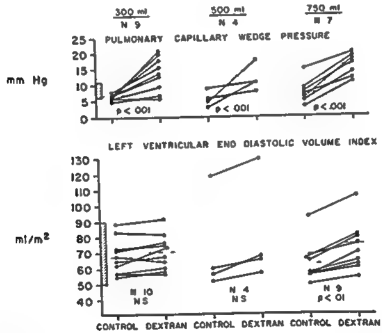

Fig 3 Effect of dextran infusion on pulmonary capillary wedge pressure and left ventricular end diastolic volume index

midpoint of the left ventricle and connected to a high frequency ratemeter and rapid response strip-chart recorder as described in detail previously[1, 3] ^{113m}Indium was injected into the superior vena cava and the scintillation probe recorded its passage through the central circulation producing a twin peaked time activity curve The first peak represents passage of the bolus of radioactivity through the right ventricle the second peak passage through the left ventricle The recording was repeated after 5 minutes to obtain the concentration after mixing and a blood sample was taken at this time to determine total blood volume From these two measurements cardiac output was determined by dilutional analysis [12]

Left ventricular stroke volume was calculated from cardiac output divided by heart rate Left ventricular ejection fraction was measured from the left ventricular part of the time activity curve

Effect of dextran loading on left ventricular performance in chronic obstructive pulmonary disease

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The status of left ventricular performance in chronic obstructive pulmonary disease (COPD) is still controversial It has been suggested that left ventricular dysfunction may occur as a complication of COPD[1-5] Other investigators have found no evidence of left ventricular failure in patients with COPD[6-10]

It is also possible that in COPD the left ventricle receives insufficient pulmonary venous return due to right ventricular dysfunction thus, it is volume underloaded The purpose of this study was to assess left ventricular performance at rest, to determine whether the left ventricle is volume underloaded and to ascertain whether the stress of a volume load might reveal latent left ventricular dysfunction in individuals with COPD

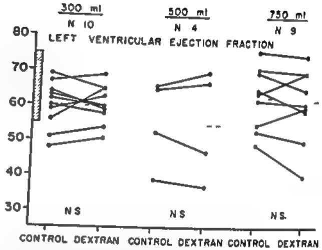

Fig 1 Left ventricular ejection fraction response to dextran infusion Shaded bar represents the normal range *N* = number of subjects *N S* = not significant

Materials and methods

Twenty three men, 53 to 75 years of age (average, 62), with severe chronic obstructive pulmonary disease were studied Subjects 10 14 16 and 19 also had clinically evident coronary artery disease (angina history of myocardial infarction abnormal q wave on the electrocardiogram [ECG]) None was receiving digitalis or diuretics at the time of the study and all were in stable compensated clinical state Prior to the study pulmonary function tests were performed and arterial blood gases determined while the subjects were breathing ambient air Supplemental oxygen was administered by nasal cannula during the study when needed to maintain normal arterial oxygen saturation (> 90 per cent)

A Swan Ganz catheter was utilized in each case to measure pulmonary artery (PA) and pulmonary capillary wedge (PCW) pressures Brachial artery pressure and a standard limb lead of the ECG were also recorded Quantitative radiocardiography[11-13] with a portable scintillation probe (5 by 5 cm sodium iodide crystal) and the radionuclide ^{113m}Indium was employed to measure cardiac output left ventricular ejection fraction (LVEF) stroke volume and left ventricular end diastolic volume ^{113} Indium rapidly binds to transferrin and thus can be used to determine total blood volume and cardiac output

A scintillation probe was positioned over the

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DLCO		Pao (mm Hg)	Paco (mm Hg)
Ml/min/mm Hg	% pred.		
4.5	(30)	61	29
–	–	68	30
5.6	(49)	64	41
9 5	([illegible]7)	4	28
3	(15)	53	40
10	([illegible]6)	[illegible]9	49
22	(96)	50	48
3	(12)	51	36
13	(46)	41	47
–	–	[illegible]9	29
11	(4)	66	45
–	–	69	38
4	(2[illegible])	6[illegible]	45
16	(56)	39	34
16	(6[illegible])	[illegible]8	46
8	(38)	4	4[illegible]
20	(69)	62	48
13	(60)	40	41
14	(51)	44	45
[illegible]	([illegible]3)	31	82
4	(14)	30	4[illegible]
1[illegible]	([illegible])	0	28
12	(53)	[illegible]8	[illegible]8
11 ± 1	(54 ± 5)	56 ± 1	41 ± 2

ments were then repeated 5 minutes after the dextran infusion had been completed Ten patients received 300 ml four 500 ml and nine [illegible]00 ml of dextran respectively

Results

Table I indicates that the subjects of this study had severe chronic obstructive pulmonary disease Pulmonary function tests revealed a forced expiratory volume in one second (FEV_1) of 1 07 ± 0 08 L (mean ± S E M) and FEV /FVC (forced vital capacity) 37 ± 2 per cent Arterial Po_2 while breathing ambient air ranged from 30 to [illegible]8 mm Hg (average 56) and arterial Pco_2 28 to 82 mm Hg (average 41)

Left ventricular ejection fraction is an important reproducible measure of systolic ventricular function [5,17] In 19 subjects with COPD alone resting LVEF was 62 ± 2 per cent (mean ± S E M normal 55 to 75 per cent) However in the four subjects with COPD and coronary artery disease mean LVEF was reduced (51 ± 4 5 per cent) Left ventricular ejection fraction for the total group of 23 subjects was normal (60 ± 2 per cent)

Basal mean measurements of stroke volume index (39 ± 1 ml per square meter normal 32 to 58 ml per square meter) left ventricular end diastolic volume index (66 ± [illegible] ml per square meter normal 50 to 90 ml per square meter), and cardiac index (3 35 ± 0 12 L per minute per square meter normal 2 8 to 4 2 L per minute per square meter) for the 23 subjects were all normal [illegible] Mean pulmonary capillary wedge pressure (8 ± 0 8 mm Hg normal [illegible] to 12 mm Hg) was also normal [illegible] However mean pulmonary artery pressure (26 ± 2 mm Hg normal 13 to 18 mm Hg) was elevated indicating the severity of lung disease in the group studied [23]

Results of dextran infusion are summarized in Table II Following volume loading left ventricular ejection fraction should be maintained and may increase slightly deterioration in mean LVEF for the group would indicate left ventricular dysfunction [illegible] In the present study LVEF was maintained in those subjects receiving 300 500 or 750 ml with no significant change in any of the three groups (Fig 1) Cardiac index stroke volume index left ventricular end-diastolic volume index and pulmonary capillary wedge pressure all normally increase significantly following volume loading [illegible] If left ventricular dysfunction were present mean CI and SVI would decrease with volume loading [illegible] Both CI and SVI increased significantly with infusion of 750 ml of dextran however with lesser volume infusions the increase was not significant (Fig 2) Also LVEDVI increased significantly only following a 750 ml infusion (Fig 3) Pulmonary capillary wedge pressure (Fig 3) and mean PA pressure (Fig 4) both increased significantly with 300 500 and 750 ml dextran infusions Pulse rate and mean arterial pressure normally do not change with dextran infusions less than 1 000 ml However following infusions of 1 000 to 1 500 ml mean arterial pressure has been shown to increase [26] In this study pulse rate and arterial pressure did not change significantly in any of the three groups (Table II)

Discussion

This study demonstrates that at rest and following the stress of volume loading left ventri

Table I Results of pulmonary function tests*

Pt No	VC L	VC % pred	FEV$_1$ L	FEV$_1$ % pred	FEV$_1$/VC (%)	RV L	RV % pred	TLC L	TLC % pr
1	2 47	(84)	0 98	(49)	39	6 10	(149)	5 00	(1?
2	2 73	(83)	0 99	(46)	36	—	—	—	—
3	1 79	(44)	0 74	(25)	41	6 15	(280)	7 58	(12
4	2 88	(65)	1 24	(39)	43	2 47	(128)	6 00	(10
[illegible]	2 16	(52)	0 81	(26)	38	4 65	(189)	6 52	(10
6	3 22	(73)	1 61	(51)	50	4 60	(196)	7 80	(11
7	2 66	(67)	1 11	(45)	42	2 28	(114)	4 94	(8
8	3 33	(77)	0 79	(23)	24	4 44	(179)	7 75	(11
9	3 25	(71)	1 09	(33)	34	4 71	(195)	7 95	(11
10	4 54	(92)	2 05	(58)	45	—	—	—	—
11	2 57	(53)	0 74	(21)	29	7 12	(247)	8 93	(13
12	2 92	(62)	0 98	(30)	34	6 58	(258)	9 48	(13
13	1 96	(58)	0 82	(35)	42	4 29	(193)	6 25	(11
14	4 83	(121)	1 56	(59)	32	3 69	(143)	8 52	(13
15	2 20	(52)	0 63	(22)	29	6 33	(242)	8 50	(12
16	2 30	(69)	0 84	(37)	36	4 24	(190)	6 56	(11
17	4 13	(90)	1 30	(38)	42	7 61	(314)	1 18	(16
18	3 29	(86)	0 83	(34)	33	5 10	(124)	6 77	(10
19	3 20	(79)	1 34	(49)	42	4 33	(171)	7 55	(11
20	2 12	(52)	0 63	(22)	39	6 05	(257)	8 17	(1?
21	1 84	(53)	0 48	(19)	26	—	—	—	—
[illegible]	3 40	(76)	1 80	(64)	53	4 48	(147)	8 58	(11
23	3 48	(88)	1 35	(48)	39	4 19	(185)	7 68	(1?
Mean ± S E M	2 92 ± 0 17	(72 ± 4)	1 07 ± 08	(38 ± 3)	37 ± 2	4 97 ± 0 32	(195 ± 12)	7 09 ± 0 42	(118 ±

Abbreviations VC vital capacity FEV forced expiratory volume in 1 sec RV residual volume TLC total lung capacity DLCO diffusing capacity carbon monoxide Pao partial pressure of oxygen in arterial blood (Denver normal 0 ± 5 mm Hg) Paco partial pressure of carbon dioxide in arte blood (Denver normal 36 ± 2 mm Hg) L liters

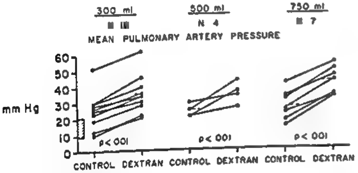

Fig 4 Effect of dextran infusion on mean pulmonary artery pressure

as the fractional fall in count rate from end diastole to end systole divided by the end diastolic count rate [11, 12] Left ventricular end diastolic volume (LVEDV) was calculated from LVEF and left ventricular stroke volume (LVSV) by the equation

$$\text{LVEDV} = \frac{\text{LVSV}}{\text{LVEF}}$$

Cardiac index (CI) stroke volume index (SVI) and left ventricular end diastolic volume index (LVEDVI) were calculated using the patient s body surface area

The accuracy of quantitative radiography has been described in detail elsewhere [11, 12] Steele and associates[12] have obtained a good correlation between left ventricular ejection fraction determined by the scintillation probe and cine ventriculography in 36 patients ($r = 0.90$, $P < 0.001$) Recently Schelbert and associates[13] have obtained a similar, good correlation in LVEF utilizing ^{99m}Tc labeled to human serum albumin and a gamma scintillation camera Cardiac output was measured by Steele and associates[12] in 35 patients with ^{113}indium and the scintillation probe and with indocyanine green dye with a good correlation ($r = 0.78$ $P < 0.001$)

After control measurements were made, dextran 40 in glucose was infused intravenously at a rate of 15 to 20 ml per minute [11] All measure

decreased left ventricular preload in patients with chronic cor pulmonale

Left ventricular failure seems to be very uncommon in patients with chronic obstructive pulmonary disease and when it does occur in such patients it is likely to be due to coexistent coronary artery disease

Summary

The status of left ventricular function in patients with chronic obstructive pulmonary disease remains controversial With a radionuclide technique left ventricular ejection fraction left ventricular end diastolic volume cardiac output and stroke volume were measured at rest and following infusion of dextran in 23 men with severe COPD

Resting mean LVEF was normal in 19 subjects with COPD alone four with COPD and coronary artery disease had a depressed mean LVEF Left ventricular end diastolic volume index and pulmonary capillary wedge pressure were both normal at rest indicating that the left ventricle was not volume underloaded There was a normal response to dextran infusion (750 ml) with no deterioration in LVEF and a significant increase in cardiac index stroke volume index LVEDVI and PCW These data suggest that at rest and following volume loading with dextran left ventricular function is normal in patients with COPD

References

1. Rao, B J Cohn K E Eldridge F L and Hancock, C W Left ventricular failure secondary to chronic pulmonary disease Am J Med 45 229 1968
2. Baum, G L Schwartz A Llamas, R and Castillo C Left ventricular function in chronic obstructive lung disease N Engl J Med 285 361 1971
3. Michelson N Bilateral ventricular hypertrophy due to chronic pulmonary disease Dis Chest 38 435 1960
4. Fluck D C Chandrasekar R G and Gardner F V Left ventricular hypertrophy in chronic bronchitis Br Heart J 28 92 1966
5. Edwards, C W Left ventricular hypertrophy in emphysema Thorax 29 75 1974
6. Murphy M L Adamson J and Hutchenson F Left ventricular hypertrophy in patients with chronic bronchitis and emphysema Ann Intern Med 81 307 1974
7. Harvey R M Ferrer M I Richards, D W and Cournand, A Seminars on pulmonary physiology Influence of chronic pulmonary disease on the heart and circulation Am J Med 10 719 1951
8. Bove K E and Scott R C The anatomy of chronic cor pulmonale secondary to intrinsic lung disease Prog Cardiovasc Dis 9 227 1966
9. Khaja F and Parker J O Right and left ventricular performance in chronic obstructive lung disease Am Heart J 82 319 1971
10. Williams, S F Jr Childress, R H, Boyd D L, Higgs, L M and Behnke R H Left ventricular function in patients with chronic obstructive pulmonary disease J Clin Invest 47 1143 1968
11. Steele P P, Ellis J H Jr Van Dyke D Sutton F, Creagh E and Davies, H Left ventricular ejection fraction in chronic obstructive pulmonary disease Am J Med 59 21 1975
12. Steele P P, Van Dyke D V, Trow R S, Anger H O, and Davies H Simple and safe bedside method for serial measurement of left ventricular ejection fraction cardiac output, and pulmonary blood volume Br Heart J 36 122, 1974
13. Schelbert, H R Verba, J W Johnson A D, Brock, G W Alazraki, N P Rose E J and Ashburn W L Nontraumatic determination of left ventricular ejection fraction by radionuclide angiography Circulation 51 902, 1975
14. Enson Y Schmidt D H, Ferrer M I, and Harvey R M The effect of acutely induced hypervolemia on resistance to pulmonary blood flow and pulmonary arterial compliance in patients with chronic obstructive lung disease Am J Med. 57 395 1974
15. McAnulty J H Kremkau E L Rosch, J, Hattenhauer M T and Rahimtoola S H Spontaneous changes in left ventricular function between sequential studies, Am J Cardiol. 34 23, 1974
16. Kreulen T H Bove A A McDonough, M T, Sands, M J and Spann J F The evaluation of left ventricular function in man a comparison of methods, Circulation 51 677 1975
17. Cohn P F Levine J A, Bergeron G L, and Gorlin R. Reproducibility of the angiographic left ventricular ejection fraction Circulation 48 (Suppl. IV) 86 1973
18. Kennedy J W Baxley W A, Figley M M, Dodge H T and Blackmon J R Quantitative angiocardiography I The normal left ventricle in man Circulation 34 272 1966
19. Brandfonbrener M Landowne M and Schock, N W Changes in cardiac output with age Circulation 12 557 1955
20. Granath A and Strandell, T Relationship between intravascular pressures at rest and during exercise in supine position and some arthropometric data in healthy old men Acta Med Scand 176 447 1964
21. Dexter L Dow J W Haynes, F W, Whittenberger J L. Ferris, B G Goodale W T and Hellems, H. F Studies of the pulmonary circulation in man at rest J Clin Invest 29 602 1950
22. Dexter L Whittenberger J L, Haynes, F W, Goodale W T Gorlin R and Sawyer C G Effect of exercise on circulatory dynamics of normal individuals, J Appl. Physiol 3 439 1951
23. Reeves, J T and Grover R F High altitude pulmonary hypertension and pulmonary edema *in* Yu P and Goodwin J editors Progress in cardiology Philadelphia, 1975 Lea & Febiger Publishers.
24. Mitchell J H Wildenthal, K and Mullins C B Geometrical studies on the left ventricle utilizing biplane cinefluorography Fed. Proc 28 1334 1969
25. Krayenbuehl H P Blussman W D Turina, M and Luthy E Is the ejection fraction an index of myocardial contractility? Cardiologica 53 1 1968
26. Holt J P Effect of plethora and hemorrhage on left ventricular volume and pressure Circ Res. 5 273 1957
27. Sanghvi, V R Khaja F Mark, A L, and Parker J O Effects of blood volume expansion on left ventricular

Table II Effect of dextran infusion in subjects with chronic obstructive pulmonary disease*

Vol infused (ml)	No	Control	Post infusion
LVEF (%)			
300	10	60 ± 2†	60 ± 2
500	4	56 ± 7	55 ± 7
750	[illegible]	63 ± 3	62 ± 4
SVI (ml/M²)			
300	10	40 ± 2	42 ± 2
500	4	37 ± 3	40 ± 4
750	9	38 ± 2	43 ± 2‡
CI (L/min/M²)			
300	10	3 44 ± 19	3 61 ± 0 22
500	4	3 25 ± 24	3 56 ± 0 23
750	9	3 30 ± 22	3 61 ± 0 25§
LVEDVI (ml/M)			
300	10	67 ± 4	70 ± 4
500	4	71 ± 16	79 ± 17
750	9	62 ± 4	74 ± 7‡
PCW (mm Hg)			
300	9	7 ± 1	14 ± 2‖
500	4	6 ± 1	12 ± 2‖
750	7	8 ± 1	16 ± 1‖
PA (mm Hg)			
300	10	26 ± 4	36 ± 4‖
500	4	25 ± 2	36 ± 4‖
750	7	27 ± 4	43 ± 3‖
MAP (mm Hg)			
300	9	102 ± 4	104 ± 3
500	4	93 ± 5	93 ± [illegible]
750	8	98 ± 4	105 ± 1
HR			
300	10	87 ± 3	87 ± 3
500	4	88 ± 3	90 ± 6
750	9	87 ± 3	85 ± 6

Abbreviations LVEF left ventricular ejection fraction SVI left ventricular stroke volume index CI cardiac index LVEDVI left ventricular end-diastolic volume index PCW pulmonary capillary wedge pressure PA mean pulmonary artery pressure MAP mean systemic arterial pressure HR heart rate beats per minute
†Mean ± S E M
‡Mean significantly different from control $P < 0\ 01$
§$P < 0\ 05$
‖$P < 0\ 001$

cular performance assessed by left ventricular ejection fraction, stroke volume index and cardiac index [illegible] normal in patients with chronic obstructive pulmonary disease alone Significant left ventricular dysfunction would have been revealed if mean LVEF SVI, and CI had been low at rest or had deteriorated following volume loading An exception noted in this study was among subjects with COPD and clinically evident coronary artery disease who had a depressed resting mean left ventricular ejection fraction

Several investigators have suggested that lef ventricular dysfunction occurs secondary t chronic obstructive pulmonary disease[13] I support of this contention left ventricular hyper trophy has been described at autopsy in patient with chronic bronchitis and emphysema[3,5] How ever, the presence of myocardial hypertrophy does not necessarily indicate that myocardia function is depressed The hypertrophied myocar dium may function normally or supernormal ly[10,31,34]

Clinical evidence suggesting left ventricular failure has been based upon the findings of an elevated end diastolic pressure[1,2] and an abnor mal ventricular function curve following an angiotensin induced increase in afterload How ever, increased end diastolic pressure [illegible] an unre liable index of left ventricular failure[35,36] and angiotension has been shown to have a negative ionotropic effect on the heart[37,38]

Other studies have failed to reveal evidence of left ventricular dysfunction in patients with chronic bronchitis and emphysema[6,11] Recently Murphy and associates[6] examined the incidence of left ventricular hypertrophy at autopsy among 72 patients with COPD and in most cases did not find it unless hypertension or arteriosclerotic heart disease or both were present In other series left ventricular hypertrophy has not been observed at autopsy[7,8] Khaja and Parker[9] found a normal left ventricular end diastolic pressure at rest and during exercise in patients with COPD Williams and associates[10] examined the response of stroke volume index stroke work index and stroke power index to methoxamine induced increase in afterload and found a normal rise in these indices in 16 patients with COPD Steele and associates[11] reported that left ventricular ejection fraction generally was normal among patients with severe COPD in a stable state unless concomitant coronary artery disease was present Our data extend that observation to include a normal mean ejection fraction in subjects with COPD even after stressing the left ventricle with volume loading

The data from this study also indicate that the left ventricle is not volume underloaded in patients with COPD Basal, mean pulmonary capillary wedge pressure and left ventricular end diastolic volume index were normal in the present study These findings are similar to those of Frank and associates[3] who found no evidence of a

Reactive hyperemia: An index of the significance of coronary stenoses

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Several studies[1-3] indicate that severe stenosis with greater than 80 per cent reduction in arterial cross-sectional area must be present before distal blood flow and arterial pressures are significantly reduced. When such "critical" degrees of stenosis are created in the coronary artery, objective evidence of myocardial ischemia appears. Myocardial K efflux, lactate production, alteration in the ST segment, and more complete extraction of arterial oxygen by the myocardium are the consequences of such stenosis.[4-6] Elliott and associates,[7] however, suggested that important changes in coronary blood flow autoregulation might occur with less than "critical" stenosis and might limit vascular reactivity during increased blood flow following increased metabolic demand.

The object of the current investigation was to study the quantitative effects of measured degrees and varying lengths of coronary arterial stenoses, including those of less than "critical" severity. The coronary flow reserve, as elicited by the reactive hyperemic response to transient coronary artery occlusion, was utilized to judge the physiological significance of the narrowings.

Methods

Experiments were performed on 15 anesthetized mongrel dogs. Anesthesia was induced with pentobarbital (30 mg. per kilogram) and respiration was maintained with a Harvard positive pressure ventilator using room air. A left thoracotomy was performed through the fifth intercostal space, the pericardium incised, and the heart suspended in a pericardial cradle.

The proximal portion of the left anterior descending coronary artery was dissected free with preservation of any side branches and a suitably sized electromagnetic flow probe was applied (Carolina Medical Electronics, Inc.). A modified metal Goldblatt clamp (4.5 mm. in length) was applied proximal to the flow probe, allowing stenoses of varying severity to be created. The reactive hyperemic response to a 15 second occlusion was examined before, as control, and after creation of the stenosis. Records of mean coronary flow were recorded at a paper speed of 0.5 mm. per second with a Sanborn 350 recorder.

A minimum of 3 minutes between occlusions was allowed so that the flow could return to the preocclusion level. Heart rate, measured with a conventional electrocardiogram (ECG), aortic pressure, measured with a polyethylene catheter connected to a Statham P23Gb transducer, and aortic flow, measured with an electromagnetic flow probe (Carolina Medical Electronics, Inc.) were recorded to assess preparation stability.* These data allowed convenient analysis of the response and calculation of the flow debt, peak reactive hyperemia, total reactive hyperemia, and flow debt repayment as described by Coffman and Gregg. Phasic coronary flow was recorded at 10 mm. per second so that changes in the diastolic and systolic flows could be detected.

After the animal had been put to death, the heart was removed, the left coronary artery was

*In the control state and for all stenoses at least two periods of occlusion and reactive hyperemia were studied to assess reproducibility of the measurement.

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hemodynamics in man Circulation 46 780 1972
28 Schnabel T G Eliasch H Thomasson B and Werko L The effect of experimentally induced by hypervolemia on cardiac function in normal subjects and patients with mitral stenosis J Clin Invest. 38 117 1959
29 Witham A C Fleming J W and Bloom W L The effect of the intravenous administration of dextran on cardiac output and other circulatory dynamics J Clin Invest 30 897 1951
30 Fleming J W and Bloom W L Further observations on the hemodynamic effect of plasma volume expansion by dextran J Clin Invest 36 1233 1957
31 Grimm A F Kubota R and Whitehorn W V Properties of myocardium in cardiomegaly Circ Res 12 118 1963
32 Beznak M Cardiac output in rats during the development of cardiac hypertrophy Circ Res 6 207 1958
33 Whitehorn W V and Grimmenga A F Effects on exercise on properties of the myocardium J Lab Clin Med 48 959 1956
34 Kerr A Winterberger A R and Giambatista M Tension developed by papillary muscles from hypertrophied rat hearts, Circ. Res. 9 103 1961
35 Braunwald E and Ross J Jr Editorial The ventricular end diastolic pressure appraisal of its value in recognition of ventricular failure in man Am J Med 34 147 1963
36 Holt, J P Editorial review Ventricular end-diastolic volume and transmural pressure Cardiologica 50 281 1967
37 Frank M J Nadimi M Casanegia P Stein P and Pekaar R The effect of angiotensin on myocardial function Am J Physiol 218 1267 1970
38 Ahmed S S Levinson G E Weisse A B and Regan T J Angiotensin and myocardial contractility Clin Res 20 853 1972
39 Frank M J Weisse A B Moschos C B and Levinson, G E Left ventricular function metabolism and blood flow in chronic cor pulmonale Circulation 47 798 1973

Regression equations and lines were obtained om these data with the least squares method hese confirmed that the mean values obtained r the 3 mm. length were significantly different om those of the 9 mm length in the range 40 to per cent luminal cross section area reduction < 0.05) A similar statistically significant fference was not found between 6 and 9 mm ngths perhaps because of the small number of servations.

scussion

These studies have applied and extended infor mation concerning the influence of arterial narrowing on resting and coronary flow reserve as elicited with the use of reactive hyperemic response as a physiological stimulus

Mann and associates[1] showed that increasing stenosis has the same effect on steady as on pulsatile flow This suggests that the laws of fluid mechanics, established in vitro may be applied when considering the influence of a stenosis on arterial flow and pressure May and associates studied the pressure flow response to increasing stenosis to critical levels in vivo measuring changes in the iliac arteries of dogs They found that pressure drop and flow reduction occurred simultaneously and varied inversely with increasing stenosis Other studies[3, 11] also outlined factors which influence the degree of stenosis which will produce these changes These factors include the velocity of blood in the prestenotic artery the cross sectional luminal area of the unstenosed and stenosed vessel and the length of the stenosis

In our study these factors were evaluated in relation to coronary arterial flow The results from the 3 to 4 5 mm length series confirm that severe stenosis (> 70 per cent) is required to reduce mean resting flow In addition the 3 6 and 9 mm length narrowings show that increasing length reduces the severity of lesion required to reduce resting flow and alter the reactive hyperemic response Hence these studies confirm the observation that measurement of resting flow alone is insensitive to define degrees of narrowings which have potential functional significance

We utilized temporary occlusion and study of the reactive hyperemic response as a functional test. Release of a 15 second coronary arterial occlusion results in a rapid predictable hyperemic response which provides a sensitive and reproducible stimulus to test vascular reactivity[10-15] Serial responses provoked remarkably reproducible results in this study

The peak hyperemic flow elicited is similar in magnitude to that produced by heavy exercise excitement or coronary vasodilator administration in the dog Fifteen second occlusions were chosen because little over all hemodynamic effect and no electrical instability results Coronary flow returns to its preocclusion level within 2 minutes allowing repeated study

The increase in flow produced affects both systolic and diastolic phases of coronary flow The systolic increase is nearly maximal upon release whereas diastolic flow increases more slowly to its maximum and persists longer than the systolic response We recorded these phasic changes in many studies but have expressed the change by measurement of mean flows which encompass changes in both phases Mean flow measurement facilitates the measurement of flow debt peak and total reactive hyperemia

The results of this study show that the coronary flow reserve as elicited using reactive hyperemia is reduced by degrees of stenosis insufficient to alter resting flow When the narrowing is critical, i e reduces resting flow the reactive hyperemic response is minimal or completely abolished This latter finding is in agreement with the observations of others [17] The present study provides quantitative information about these relationships In addition it demonstrates that when similar degrees of stenosis are applied increasing the length of stenosis causes additional reduction in the reactive hyperemic response

The mechanism(s) which are responsible for the effects of stenosis on resting coronary flow and reactive hyperemia are not clearly understood Coronary autoregulation which provides the intrinsic control system to stabilize blood flow and maintain tissue oxygenation may be the explanation[2, 9] In the presence of a constant perfusion pressure changes in flow are controlled by resistance arterioles and precapillary sphincters. At rest in an unstenosed vessel these units have basal myogenic activity The arterioles show partial constriction and many sphincters remain closed In response to increased oxygen demand both elements have the ability to dilate and a

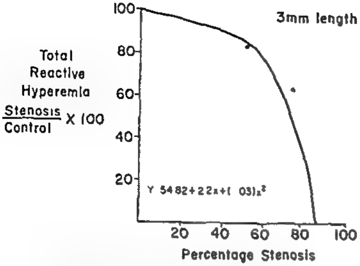

Fig 1 Plot of total reactive hyperemia (TRH) response vs degree of arterial narrowing for 3 mm length occluders The poststenotic change in TRH is expressed *as a per cent of the* control (prestenotic) value (see text for details)

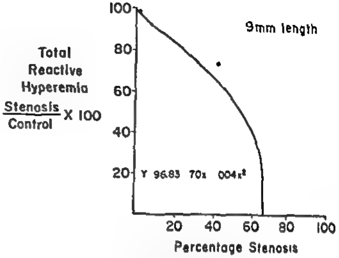

Fig 2 Plot of total reactive hyperemic response vs degree of arterial narrowing for 9 mm length occluders (see text for *details)*

injected with a barium gelatin formalin mixture[11] and postmortem coronary arteriograms were obtained in multiple views After magnification, the degree of stenosis was assessed and expressed as the percentage reduction in cross sectional area compared to the unstenosed vessel proximal to the occluder

Ten additional dogs were studied to assess the effect of the length of stenosis on the reactive hyperemic response using the same protocol Radiolucent plastic screw clamps of 3 6 and 9 mm lengths were utilized and allowed several degrees of stenoses to be calculated in a single preparation, since selective coronary arteriograms could be performed in the postmortem specimen and serial narrowings and measurements made

Results

Resting left anterior descending coronary artery flow ranged from 15 to 40 ml per minute In the control prestenotic state, the temporary occlusion produced a peak reactive flow range of 2 7 to 7 3 times resting flow Total reactive hyperemia always overpaid the flow debt the ratio ranging from 3 4 to 12 2 The variation around the mean value for total reactive hyperemia was 4 6 per cent and the variation in peak reactive hyperemia was 2 7 per cent

Increasing the length of a stenosis reduced resting flows at a lesser degree of stenosis The flow alterations produced by 3 and 4 5 mm narrowings were not significantly different statistically Stenoses by a 3 mm (or 4 5 mm) clamp reduced resting flow when the luminal cross section area was narrowed by 70 to 93 per cent (seven observations) Narrowings of 6 mm length reduced resting flow when the cross sectional luminal area was reduced by 56, 67 and 68 per cent in three separate studies Resting flow was reduced by narrowings of 41 and 60 per cent in two studies done with a stenosis 9 mm long Comparing the 3 to 4 5 mm length narrowings with 6 to 9 mm length narrowings the difference in the mean values is significant ($p < 0.05$)

Figs 1 and 2 illustrate the effect of different lengths of stenoses on the total reactive hyperemic response in animals studied with the 3 and 9 mm length narrowings Similar values are found with flow debt repayment instead of total reactive hyperemia which provides allowance for the reactive hyperemic response relative to resting flow Resting flow reduction occurred at the degree of narrowing abolishing reactive hyperemia (approximately 85 per cent for 3 mm length stenoses) In contrast the 9 mm length stenoses reduced total reactive hyperemia by greater amounts at each degree of stenosis and the total reactive hyperemic response was completely abolished at approximately 65 per cent cross sectional area reduction As with the 3 mm length stenoses resting flow diminished at approximately the same degree of stenosis at which the reactive hyperemic response was abolished

Regression equations and lines were obtained from these data with the least squares method. These confirmed that the mean values obtained for the 3 mm. length were significantly different from those of the 9 mm. length in the range 40 to 0 per cent luminal cross section area reduction ($p < 0.05$). A similar statistically significant difference was not found between 6 and 9 mm. lengths, perhaps because of the small number of observations.

Discussion

These studies have applied and extended information concerning the influence of arterial narrowing on resting and coronary flow reserve as elicited with the use of reactive hyperemic response as a physiological stimulus.

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In our study these factors were evaluated in relation to coronary arterial flow. The results from the 3 to 4.5 mm. length series confirm that severe stenosis (> 70 per cent) is required to reduce mean resting flow. In addition the 3, 6 and 9 mm. length narrowings show that increasing length reduces the severity of lesion required to reduce resting flow and alter the reactive hyperemic response. Hence these studies confirm the observation that measurement of resting flow alone is insensitive to define degrees of narrowings which have potential functional significance.

We utilized temporary occlusion and study of the reactive hyperemic response as a functional test. Release of a 15 second coronary arterial occlusion results in a rapid, predictable hyperemic response which provides a sensitive and reproducible stimulus to test vascular reactivity.[10, 15] Serial responses provoked remarkably reproducible results in this study.

The peak hyperemic flow elicited is similar in magnitude to that produced by heavy exercise, excitement, or coronary vasodilator administration in the dog.[16] Fifteen second occlusions were chosen because little overall hemodynamic effect and no electrical instability results. Coronary flow returns to its preocclusion level within [illegible] minutes allowing repeated study.

The increase in flow produced affects both systolic and diastolic phases of coronary flow. The systolic increase is nearly maximal upon release whereas diastolic flow increases more slowly to its maximum and persists longer than the systolic response. We recorded these phasic changes in many studies but have expressed the change by measurement of mean flows which encompass changes in both phases. Mean flow measurement facilitates the measurement of flow debt, peak, and total reactive hyperemia.

The results of this study show that the coronary flow reserve as elicited using reactive hyperemia is reduced by degrees of stenosis insufficient to alter resting flow. When the narrowing is critical, i.e., reduces resting flow, the reactive hyperemic response is minimal or completely abolished. This latter finding is in agreement with the observations of others.[1, 7] The present study provides quantitative information about these relationships. In addition it demonstrates that when similar degrees of stenosis are applied, increasing the length of stenosis causes additional reduction in the reactive hyperemic response.

The mechanism(s) which are responsible for the effects of stenosis on resting coronary flow and reactive hyperemia are not clearly understood. Coronary autoregulation which provides the intrinsic control system to stabilize blood flow and maintain tissue oxygenation may be the explanation.[1, 8] In the presence of a constant perfusion pressure changes in flow are controlled by resistance arterioles and precapillary sphincters. At rest in an unstenosed vessel these units have basal myogenic activity. The arterioles show partial constriction and many sphincters remain closed. In response to increased oxygen demand both elements have the ability to dilate and a

potential coronary flow reserve exists Following the application of a coronary arterial stenosis, resting flow is maintained by vascular relaxation with arteriolar dilatation and an increase in the effective capillary density by recruitment This occurs in a stepwise fashion with increasing stenosis until maximum peripheral dilatation is present when a further reduction in the arterial lumen is critical and reduces resting flow

During a temporary occlusion in an unstenosed vessel, marked recruitment of capillaries occurs by opening of precapillary sphincters This allows a massive increase in flow on release [9] This reactive hyperemia is attentuated following the application of a stenosis as recruitment of some of the reserve capillaries has already occurred Some of the coronary flow reserve is already "used up" leading to a reduced response on release of the occlusion At the 'critical' degree of stenoses the bed is maximally dilated, no reactive hyperemia occurs, and any further reduction in lumen caliber will reduce resting flow

The results of this study suggests that measurement of the reactive hyperemic response provides an experimental method to determine the quantitative influence of a stenosis on coronary autoregulation even when resting flow is unimpaired It has clinical relevance and emphasizes that assessment of the hemodynamic importance of a stenosis seen by arteriography must take into account the length as well as the severity of narrowings

Summary

Coronary arterial stenosis of varying severity and length were created in open chest dogs The reactive hyperemic responses (RHR) to 15 second occlusions were used to produce flow increases and judge the physiological significance of the narrowings RHR are sensitive indices of functional impairment when resting flow is unchanged It was demonstrated that the length as well as the severity is important in assessing physiological significance by evaluation of narrowings 3 to 9 mm long

REFERENCES

1 Mann F G Baldes E J Essex H E and Herrick J F The effect on the blood flow of decreasing the lumen of a blood vessel Surgery 4 249 1938
2 Cannon J A Frankenberg H L Herrold G and Lobpreis E L Experience with a new electro magnetic flow meter for use in blood flow determinations in surgery Ann Surg 152 653 1960
3 Schenk, W G Martin J W and Menno A D Hemodynamics of experimental coarctation of the aorta Ann Surg 153 163 1961
4 Haimovici H and Zinicola N Experimental renal artery stenosis diagnostic significance of arterial hemo dynamics J Cardiovasc Surg 3 259 1962
5 May A G Deweese J A Rob C G and Van de Berg I Critical arterial stenosis Surgery 54 250 1963
6 Shea T M Case R B Dirmksian G Piotrewski S F and Watson R M Anaerobic myocardial metabolism Am J Physiol 203 463 1962
7 Case R B Crampton R S and Roselle H A Relation of ST-depression to myocardial potassium loss during coronary insufficiency Am J Cardiol 17 136 1966
8 Case R B and Roven R B Some considerations of coronary flow Prog Cardiovasc Dis 6 45 1963
9 Elliott E C Bloor C M Gregg D E Jones E L and Leon A S Day to day changes in coronary hemodynamics secondary to constriction of the circumflex branch of left coronary artery in conscious dogs Circ Res 22 237 1968
10 Coffman J D and Gregg D E Reactive hyperemia characteristics of myocardium Am J Physiol 119 1143 1960
11 Schlesinger M D New radiopaque mass for vascular injection Lab Invest 6 1 1957
12 May A G Deweese J A and Rob C G The hemodynamic effects of arterial stenosis Surgery 53 513 1963
13 Kindt G W and Youmans J R The effect of stricture length on critical arterial stenosis Surg Gynecol Obstet 128 729 1969
14 Rodbard S Dynamics of blood flow in stenotic vascular lesions Am Heart J 72 698 1966
15 Olsson R H and Gregg D E Myocardial reactive hyperemia in the unanesthetized dog Am J Physiol 208 224 1965
16 Khouri E M Gregg D E and Lowensohn H S Flow in the major branches of the left coronary artery during experimental coronary insufficiency in the unanesthetized dog Circ Res 23 99 1968
17 Reneman R S and Spencer M P The use of diastolic reactive hyperemia to evaluate the coronary vascular system Ann Thorac Surg 13 477 1972
18 Johnston P C Review of previous studies and current theories of autoregulation Circ Res 15(Suppl 1) 2 1964
19 Mellander S and Johansson B Control of resistance exchange and capacitance functions in the peripheral circulation Pharm Rev 20 117 1968
20 Renkin E M Hudlicka O and Sheehan R M Influence of metabolic vasodilation on blood tissue diffusion in skeletal muscle Am J Physiol 211 87 1966
21 Roselle H A Case R B and Crampton R S Alterans of the depressed ST segment during coronary insufficiency Am J Cardiol 18 200 1966

Coronary occlusion site as a determinant of the cardiac rhythm effects of atropine and vagotomy

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The use of atropine in acute myocardial infarction is currently controversial. This controversy has been sparked by recent experimental and clinical data demonstrating deleterious effects of atropine on cardiac rhythm. Studies in animals have shown that atropine administration increases the incidence of ventricular fibrillation, increases the incidence of ventricular arrhythmias, and decreases the current required to produce ventricular fibrillation. These harmful effects of atropine have all been attributed to blockade of cardiac vagal tone per se.

In all of the above experimental studies the anterior descending branch of the left coronary artery was occluded, resulting in primarily an anterior myocardial infarction. However, several studies have suggested that vagal tone is less important in anterior than in inferior infarction. The latter is associated with sinus bradycardia and heart block, both of which often respond to atropine treatment. The reason for the greater degree of vagal activation associated with inferior infarction has been postulated to be related to the proximity of cholinergic fibers to areas of ischemia in posterior regions of the heart. Anterior myocardial infarction may not stimulate these cholinergic fibers to the same degree.

Because these data have suggested a more important role of the vagus nerves in acute inferior than in anterior infarction, the present study was undertaken to examine the influence of atropine pretreatment on the cardiovascular changes produced by occlusion of the right coronary artery (experimental inferior myocardial infarction).

Methods

Adult cats, unselected as to sex and ranging in weight from 1.7 to 3.7 kilograms, were anesthetized with intravenously administered alpha chloralose (70 to 75 mg. per kilogram). A tracheotomy was performed and mechanical ventilation was instituted with a tidal volume of 20 to 25 c.c. per kilogram and a rate of 22 breaths per minute. The animals were immobilized with decamethonium bromide (0.25 mg. per kilogram intravenously) administered every 45 to 60 minutes. Catheters were inserted into the right femoral artery and vein of all animals for the purpose of measuring blood pressure and administering drugs, respectively. Body temperature was maintained between 37.0 and 38.0° C. by an infrared lamp.

The heart was exposed by excising ribs 2 through 5 on the right side. The pericardium was opened and sutured to the chest wall. Coronary occlusion was performed by isolating the right coronary artery at its origin and placing a 4-0 cotton suture under the vessel proximal to any branch points. The ligature was securely tied at the moment when occlusion was desired. At the

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Table I Influence of right coronary artery occlusion on heart rate blood pressure, aortic flow, contractile force and cardiac rhythm in control, atropinized, and vagotomized animals*

Group	*Before occlusion* Heart rate (b p m)	Mean blood pressure (mm Hg)	Aortic flow (c c /min)	Contractile force (Gm tension)	*After occlusion and prior to arrhythmia* Change in heart rate (b p m)	Change in blood pressure (mm Hg)	Change in aortic flow (c c /min)	Per cent change in contractile force	Onset of arrhythmia (min)
Control	204.2 ± 3.6 (20)†	118.6 ± 6.2 (20)	283.0 ± 20.0 (13)	12.9 ± 0.5 (5)	−30.3 ± 5.1‡ (20)	−23.1 ± 4.9‡ (20)	−48.5 ± 13.6‡ (13)	−28.0 ± 13.0‡ (5)	7.4 ± 1.4 (20)
Atropine	219.1 ± 4.5§ (15)	108.0 ± 7.1 (15)	261.8 ± 9.7 (14)	13.3 ± 0.3 (15)	−19.7 ± 6.6‡ (15)	−17.5 ± 4.8‡ (15)	−49.3 ± 10.5‡ (14)	−41.8 ± 5.1‡ (15)	9.7 ± 2.9 (10)
Vagotomy	216.5 ± 4.4§ (15)	113.5 ± 5.9 (15)	270.6 ± 10.6 (15)	13.6 ± 0.4 (15)	−14.5 ± 3.4‡§ (15)	−13.6 ± 5.3‡ (15)	−59.[illegible] ± 8.0‡ (15)	−35.6 ± 8.9‡ (15)	6.3 ± 1.3 (11)

Numbers are means ± S E

†Numbers in parentheses indicate number of animals in each group

‡p < 0.05 with paired comparisons (comparison was made between data obtained during postocclusion period and data obtained during preocclusion period)

§p < 0.05 with group comparisons (comparison was made between data obtained with either atropine or vagotomy groups vs control group)

termination of each experiment the ligature was checked to confirm the location and adequacy of occlusion

Ascending aortic flow was measured with a Biotronix BL 610 pulsed logic flowmeter utilizing a Biotronix electromagnetic flow transducer (BL 6060 E20) The probe was placed on the ascending aorta in an area which was free of connective tissue This reduced the possibility of interfering with neural elements located at the base of the aorta The flow probe was calibrated in vitro with saline, and the late diastolic level of aortic flow obtained from the pulsatile flow trace was used as the zero flow reference point

A calibrated Walton Brodie strain gauge arch was sutured to the right ventricular wall by stretching the heart muscle beneath the feet approximately 50 per cent of its resting length Right rather than left ventricular contractile force was measured since it is less sensitive to the effect of changes in preload and afterload Systemic arterial pressure heart rate and rhythm (Lead II of the electrocardiogram [ECG]) myocardial contractile force mean aortic flow and pulsatile aortic flow were continuously monitored on a Gould Brush Model 260 recorder Total peripheral resistance was calculated as peripheral resistance units (PRU)

$$PRU = \frac{\text{Mean arterial blood pressure (mm Hg)}}{\text{Mean aortic flow (ml /min)}} \times 60 \text{ (sec /min)}$$

The following three types of experiments were performed to evaluate the role of the vagus nerve on the cardiovascular changes induced by occlusion of the right coronary artery (1) occlusion was produced in 20 control animals with all nerves intact (2) occlusion was produced in 15 animals pretreated with atropine (atropine was administered intravenously in a dose of 1 mg per kilogram 15 minutes prior to occlusion) (3) occlusion was produced in 15 animals after bilateral cervical vagotomy (vagus nerves were sectioned 15 minutes prior to occlusion)

The following drugs were used alpha chloralose (Establissements Kuhlman, Paris, France), decamethonium bromide solution (Burroughs Wellcome, North Carolina), atropine sulfate (New York Quinine and Chemical Works New York City) Alpha chloralose was dissolved by heating it in distilled water, the solution was cooled to 37° C before use Atropine sulfate was dissolved in 0.85 per cent sodium chloride solution Doses of drugs were calculated and administered as the respective salt

The data were analyzed by paired comparisons and grouped Student's t test Chi square analysis for 2 × 2 contingency with the Yates correction was utilized for the arrhythmia and death rate data The criterion for statistical significance was $p < 0.05$

Results

To assess the influence of atropine on the cardiovascular events that occur with acute

Table II Influence of impaired vagal function on recovery of heart rate blood pressure aortic flow and contractile force from the effects of right coronary artery occlusion*

	Before occlusion				*One hour after occlusion*			
Group	*Heart rate (b.p.m.)*	*Mean blood pressure (mm Hg)*	*Aortic flow (c.c./min)*	*Contractile force (Gm tension)*	*Change in heart rate (b.p.m.)*	*Change in blood pressure (mm Hg)*	*Change in aortic flow (c.c./min.)*	*Per cent change in contractile force*
Control	204.2 ± 3.6 (20)†	118.6 ± 6.2 (20)	283.0 ± 20.0 (13)	12.9 ± 0.5 (5)	−25.4 ± 6.5‡ (14)	−28.6 ± 6.6‡ (14)	−57.3 ± 8.6‡ (11)	−51.3 ± 1.6‡ (3)
Atropine	219.1 ± 4.5§ (15)	108.0 ± 7.1 (15)	[illegible]61.8 ± 9.7 (14)	13.3 ± 0.3 (15)	−24.4 ± 9.4‡ (12)	−12.1 ± 5.5‡ (12)	−66.8 ± 8.4‡ (11)	−52.2 ± 6.1‡ (12)
Vagotomy	216.5 ± 4.4§ (15)	113.5 ± 5.9 (15)	2 06 ± 10.6 (15)	13.6 ± 0.4 (15)	−18.7 ± 6.1‡ (12)	−14.1 ± 5.1‡ (12)	−61.6 ± 9.6‡ (12)	−40.9 ± 10.1‡ (12)

*Numbers are means ± S.E.

†Numbers in parentheses indicate number of anim ls in each group

‡$p < 0.05$ ith paired c mparisons (mparison was made between data obtained during postocclusion period and data obtained during preocclusi n period).

§$p < 0.05$ ith group comparisons (comparison was made between d ta obt ined with ither atropine or ag tomy groups vs. control groups)

inferior myocardial infarction an experimental coronary occlusion model in cats was developed wherein the right coronary artery was ligated In 20 control animals occlusion resulted in the development of arrhythmias consisting of premature ventricular beats and/or heart block with a mean onset time of 7.4 ± 1.4 minutes Five of the 20 animals developed second or third degree atrioventricular block which appeared early (1.6 ± 0.4 minutes after occlusion) and was usually short lived (8.8 ± 1 minutes) Eighteen of the 20 including three that also exhibited atrioventricular block developed premature ventricular beats Ventricular arrhythmias developed later than atrioventricular block (9.3 ± 1.3 minutes after occlusion) and had a variable duration In 14 of the 20 animals the arrhythmia subsided within 1 hour after occlusion while in three animals the arrhythmia was still present 2 hours after occlusion The remaining three animals developed fatal ventricular fibrillation between 2 and 20 minutes after occlusion

The arrhythmias described above were always preceded by decreases in heart rate blood pressure cardiac output and contractile force These changes occurred within 2 minutes after occlusion (Table I top row) and persisted for at least 1 hour (Table II top row)

A representative experiment showing the arrhythmias and hemodynamic changes occurring with right coronary occlusion appears as Fig 1 Prior to occlusion the sinus rate was 187 beats per minute and the cardiac output was 270 ml per minute (Panel *A*) Four minutes after occlusion heart rate decreased to 180 beats per minute and depressions in cardiac output blood pressure and contractile force were apparent (Panel *B*) S T segment depression also developed Within 26 minutes after occlusion multifocal premature ventricular beats began (Panel *C*) but disappeared within 1 hour (Panel *D*) A junctional tachycardia was present at 1 hour and persisted for the duration of the observation period (i e 2 hours)

A representative experiment showing graphically the minute to minute changes in heart rate contractile force mean blood pressure, and cardiac output (aortic flow) produced by right coronary occlusion appears as part of Fig 2 As indicated decreases in heart rate contractile force mean blood pressure and aortic flow occurred simultaneously and reached a nadir within 5 minutes after occlusion These decreases were maintained over the 60 minute observation period

In contrast to the striking changes in cardiovascular indices described above no change in total peripheral resistance (TPR) was observed with right coronary occlusion TPR was 24.4 ± 1.9 PRU prior to occlusion and did not change significantly either immediately after occlusion (+0.46 ± 1.8 PRU) or at 60 minutes after occlusion (+0.87 ± 2.0 PRU)

The cardiac rhythm and hemodynamic

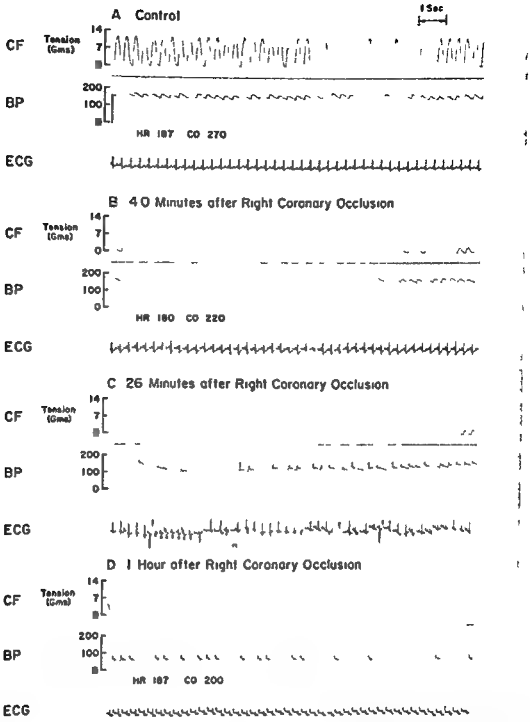

Fig 1 Effects of occlusion of the right coronary artery on the contractile force (*CF*) blood pressure (*BP*) electrocardiogram (*ECG*) and cardiac output (*CO*) in an animal with vagus nerves intact Panel *A* control recordings panels *B* *C* and *D* recordings obtained at 4 0 26 0 and 60 minutes after coronary occlusion respectively

responses evoked by right coronary occlusion in animals pretreated with atropine are summarized in Tables I and II, and Figs 3 and 4

In contrast to control animals, none of the atropine pretreated animals developed second or third degree atrioventricular block In addition premature ventricular beats occurred in only 67 per cent of the animals (i e , 10 of 15), as compared to 90 per cent of the control animals (i e , 18 o 20) Contrary to expectation atropine pretreat ment did not alter the incidence of fatal ventric ular fibrillation (20 vs 15 per cent in contro animals see Fig 3) In those animals that di develop arrhythmias the time to onset and th duration were similar to control animals (Tabl I)

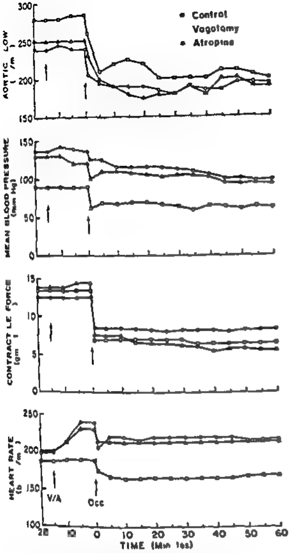

Fig. 2. Effects of right coronary occlusion (as indicated by Occ ↓) on aortic flow blood pressure contractile force and heart rate readings of an animal with its nervous system intact (*control*) an animal with its vagus nerves sectioned (*vagotomy*) and an animal pretreated with atropine (*atropine*) *V/A* at the arrow indicates the point in time either when the vagus nerves were sectioned or when the atropine was administered.

A representative experiment showing the actual cardiac rhythm changes in an animal pretreated with atropine appears as Fig 4 Prior to occlusion the sinus rate was 240 beats per minute and the cardiac output was 265 ml per minute (Panel *A*) Three and a half minutes after occlusion heart rate decreased to 214 beats per minute and depressions in cardiac output blood pressure and contractile force were apparent (Panel *B*) S T segment elevation also developed

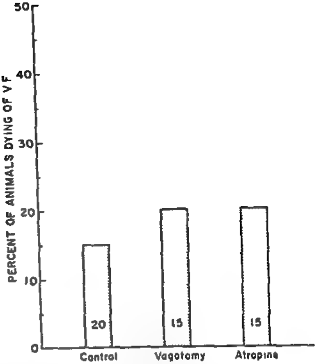

Fig 3 The effect of bilateral vagotomy and atropine administration on the incidence of death due to ventricular fibrillation after right coronary occlusion The numbers within the histograms are the number of animals in each group

Sixteen minutes after occlusion premature ventricular beats began (*Panel C*) but disappeared within 1 hour after occlusion (Panel *D*) although heart rate cardiac output blood pressure and contractile force remained depressed

The hemodynamic data obtained from the 15 animals pretreated with atropine are summarized in Tables I and II Prior to occlusion all cardiovascular indices were similar to those obtained from control animals except for a significant increase in heart rate Occlusion resulted in decreases in heart rate blood pressure cardiac output and contractile force to levels similar to those observed in the control animals This was true immediately after occlusion (Table I) as well as 1 hour after occlusion (Table II) These changes are graphically displayed for a representative experiment as part of Fig 2 The calculated TPR for the atropine pretreated group was also similar to control group prior to occlusion (i e 23 7 ± 1 6 PRU) As in control animals atropine pretreated animals did not exhibit a significant change in TPR either immediately after occlusion (+1 0 ± 1 6 PRU) or 60 minutes after occlusion (+5 7 ± 3 1 PRU)

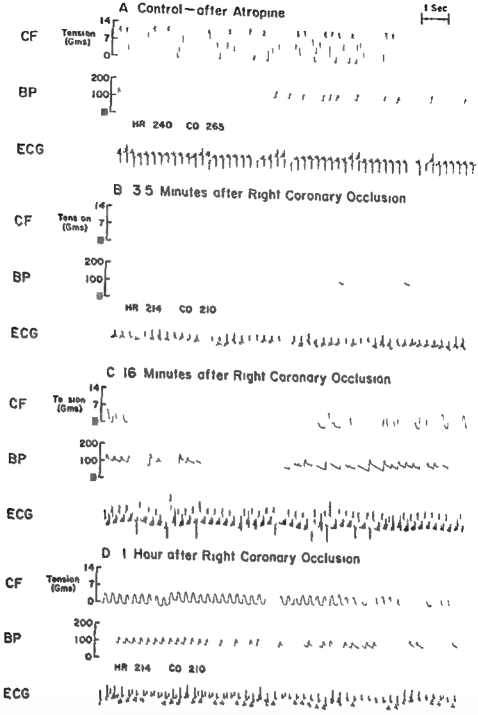

Fig 4 Effects of occlusion of the right coronary artery on the contractile force (*CF*) blood pressure (*BP*) electrocardiogram (*ECG*) and cardiac output (*CO*) after atropine administration Panel *A* control recordings panels *B* *C* and *D* recordings obtained at 3 5 16 0 and 60 minutes after coronary occlusion respectively

In 15 additional animals, bilateral vagotomy was performed prior to right coronary occlusion In contrast to controls in which all 20 animals developed arrhythmias but similar to the atropine group, approximately one fourth (i e four of 15) of the vagotomized animals never exhibited an arrhythmia Of the 11 animals with arrhythmias, all had premature ventricular beats and only one had second degree heart block (occurring 3 minutes after occlusion and persisting for 13 minutes) The time to onset of the ventricular arrhythmias was similar to that seen in the two previous groups (Table I) and the duration of the arrhythmia was again variable Vagotomy—like atropine—did not alter the incidence of fatal ventricular fibrillation (Fig 3)

As with atropine vagotomy resulted in higher heart rates (Table I) but did not alter the

decreases in blood pressure, aortic flow, and contractile force resulting from coronary occlusion (Tables I and II). However, the initial decrease in heart rate resulting from right coronary occlusion in vagotomized animals was significantly less marked than that observed in control animals (Table I). The minute to minute changes in heart rate, contractile force, blood pressure, and aortic flow that occurred with coronary occlusion in a vagotomized animal are graphically displayed as part of Fig. 3.

The initial TPR values for vagotomized animals were similar to those of the other two groups of animals studied (26.2 ± 1.3 PRU) and right coronary occlusion had no effect on this measurement. The change occurring immediately after occlusion was +2.4 ± 1.9 PRU and the change occurring 60 minutes after occlusion was +3.9 ± 1.8 PRU.

Discussion

The purpose of our study was to examine the influence of atropine pretreatment on the cardiovascular events produced by occlusion of the right coronary artery. Atropine pretreatment had no effect on the incidence of ventricular fibrillation following right coronary artery occlusion. This is in contrast to the harmful effect of atropine in animals with left anterior descending coronary artery occlusion (increased incidence of ventricular fibrillation).[5] This result contradicts the prediction one would make from clinical data demonstrating a more important role of vagal tone in inferior than in anterior infarction. But it suggests that the potential for deleterious effects of atropine in acute infarction might indeed depend on the anatomic location of the involved myocardium.

The reason for the difference between the effect of atropine on fibrillation incidence is unclear. Presumably the reason that vagal tone exerts an antifibrillatory effect with left anterior coronary artery occlusion is that Purkinje fibers are innervated by cholinergic nerves and the released acetylcholine influences the transmembrane action potential of these cells. Cholinergic innervation has been demonstrated for Purkinje cells of the *left* bundle branch of dogs and man. Furthermore, the capacity of vagal stimulation to increase *left* ventricular fibrillation threshold has been shown to be dependent on intact cholinergic fibers to the ventricular conducting system. Cholinergic innervation of the conducting system supplied by right coronary arterial blood has not to our knowledge been demonstrated. Similarly, the ability of vagal stimulation to increase *right* ventricular fibrillation threshold has not been documented. Therefore, the inability of atropine to enhance death in experimental right coronary artery ligation may be due to sparse innervation of the involved myocardium by cholinergic fibers.

Atropine pretreatment did prevent the conduction disturbances produced by right coronary ligation. Five of the 20 control animals developed heart block, but none of the atropine pretreated animals exhibited this rhythm disturbance. In contrast to our lack of knowledge regarding cholinergic innervation of the right bundle branch, there is ample evidence for rich cholinergic innervation of the A-V node. Prevention of heart block by atropine may therefore have been due to antagonism of cholinergic effects on the A-V node.

Our results suggest that right coronary occlusion increases parasympathetic effects in the A-V node region but not in ventricular myocardial tissue supplied by arterial blood from this artery. Superficially, it would appear that parasympathetic effects to the sinoatrial node were also enhanced as sinus bradycardia occurred in each animal after posterior infarction. However, the same degree of bradycardia was also observed in animals pretreated with atropine, suggesting that noncholinergic mechanisms were responsible for slowing of the sinoatrial node rate. These results are in direct contrast to those obtained with occlusion of the left anterior descending coronary artery.[5] Animals pretreated with atropine do not exhibit a slowing in sinus rate after occlusion of this vessel.

The mechanism for the sinus rate slowing seen after right coronary occlusion is unclear. Baba and colleagues have reported that occlusion of the sinoatrial node artery in the isolated perfused rat heart results in a slowing of sinus rate. They attribute the slowing in this aneural preparation to ischemia. We have found[9] that the sinoatrial node artery is a branch off the right coronary artery in 83 per cent of the cats studied. Therefore, the mechanisms of cardiac slowing seen with right coronary occlusion may be due to ischemia produced by interruption of blood flow to the sinoatrial node. This result in cats seems to

disagree with what is observed during acute inferior infarction in man According to James[16] and Webb and associates[17] bradycardia associated with inferior infarction responds to atropine treatment and therefore is probably mediated by the vagus A fallacy in this argument is that sinus rate would increase with atropine regardless of whether or not an individual has had an inferior infarction This is because the vagus nerves normally provide tone to the heart The sinoatrial node of human hearts is also primarily perfused by an artery arising from the right coronary vessel[21] and therefore, like the cat heart may develop a reduction in sinus rate because of ischemia

All of the effects of atropine seen in the present study were essentially mimicked by bilateral vagotomy except one Vagotomy did significantly antagonize but did not abolish the sinus bradycardia that initially occurred after occlusion Vagotomy had no effect on the cardiac slowing that was routinely observed one hour after occlusion In view of the lack of effect of atropine pretreatment on the cardiac slowing that occurred immediately after occlusion the partial prevention by vagotomy must be due to loss of afferent vagal tone In this regard, it is known that activation of vagal afferents will inhibit cardiac sympathetic outflow[2] and hence reduce heart rate

Extrapolating from our data obtained using anesthetized cats to the human is at best tenuous However, the heart rate and rhythm changes seen with right coronary occlusion in cats is similar to that described for man[17,23] Adgey and colleagues[3] reported that 23 per cent of the patients with inferior infarction developed atrioventricular block during the first hour after the onset of symptoms This compares closely with the 25 per cent incidence observed in our experimental study This similarity between these data is not surprising since both cats and man—unlike dogs—appear to be right coronary dominant[20] ■

The implication of our experimental findings is that deleterious effects of atropine in acute myocardial infarction may be predicted by the anatomic location of involved myocardium Our findings also raise the possibility that deleterious effects of other drugs with atropine like effects (such as procaine amide and quinidine) may be related to occlusion site

Summary

We have previously demonstrated that atropine pretreatment increases the incidence of fatal ventricular arrhythmias induced by left anterior descending coronary artery (LAD) occlusion[8] The purpose of the present study was to determine whether the deleterious effect of atropine also applies to arrhythmias induced by right coronary artery (RCA) occlusion Occlusion of the RCA resulted in ventricular arrhythmias in all 20 animals studied, followed by ventricular fibrillation in three animals (15 per cent) Right coronary occlusion also resulted in bradycardia ($-30\ 3 \pm 5\ 1$ beats per minute) and hypotension ($-23\ 1 \pm 4\ 9$ mm Hg) Pretreatment of 15 animals with atropine caused no significant increase in the incidence of ventricular fibrillation (i e, 20 per cent) In addition atropine pretreatment had no effect on the fall in heart rate and hypotension associated with RCA ligation Sectioning the vagus nerves produced results similar to atropine pretreatment with the exception that a significant portion of the bradycardia was prevented These results indicate that the increase in deaths after atropine observed in animals undergoing experimental LAD occlusion in not demonstrated with RCA occlusion The results also indicate that the potential for deleterious effects of atropine in acute infarction might depend on the anatomic location of the involved myocardium

REFERENCES

1 Epstein S E Redwood D R and Smith E R Atropine and acute myocardial infarction Circulation 45 1273 1972
2 Wallace A G Role of the vagus in acute myocardial infarction Circulation 48 669 1973
3 Sarnoff S J Heart rate in acute myocardial infarction Am J Cardiol 33 572 1974
4 Kent, K M Smith E R Redwood D R et al Electrical stability of acutely ischemic myocardium Influences of heart rate and vagal stimulation Circulation 47 291 1973
5 Corr P B and Gillis, R A Role of the vagus nerves in the cardiovascular changes induced by coronary occlusion Circulation 49 86 1974
6 Goldstein R E Karsh R B Smith E R et al Influence of atropine and of vagally mediated bradycardia on the occurrence of ventricular arrhythmias following acute coronary occlusion in closed chest dogs Circulation 47 1180 1973
7 Dokukin A V Blood pressure and pulse changes in normal and vagotomized animals during acute myocardial ischemia Fed Proc. 23 T583 1964
8 Harrison L A Harrison L H Jr Kent K M et al

Enhancement of electrical stability of acutely ischemic myocardium by edrophonium Circulation 50 J9 19/4
9. Myers, R. W Pearlman A S., Hyman R A et al Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia Circulation 49 943, 1974
10. Scherlag B J Helfant R H Haft J L. et al Electrophysiology underlying ventricular arrhythmias due to coronary ligation Am J Physiol 219 1665 [illegible]
11. Kari, R. B Orlando [illegible] Norman D et al Ineffectiveness of prophylactic atropine in decreasing arrhythmias and enhancing survival following acute coronary artery occlusion in conscious dogs. Am J Cardiol [illegible] 2/3, 19 2.
12. Morgensen, L., and Orinius, E Arrhythmic complications after parasympatholytic treatment of bradyarrhythmia in a coronary care unit Acta Med Scand 190 495 19/1
13. Zipes, D P and Knoebel [illegible] Rapid rate-dependent ventricular ectopy Chest [illegible] 1977
14. Massumi, R. A. Mason D T Amsterdam E A et al Ventricular fibrillation and tachycardia after intravenous atropine for treatment of bradycardias [illegible] Engl J Med. 287 3.6, 1972.
15. Richman S. Adverse effect of atropine during myocardial infarction J A M A 228 1414 1974
16. James, T N : Pathogenesis of arrhythmias in acute myocardial infarction Am J Cardiol 24 791 196J
17. Webb S W Adgey A A J and Pantridge J F Autonomic disturbance at onset of acute myocardial infarction Br Med J 3 89 1977
18. Kent, K. M., Epstein S E., Cooper T et al Cholinergic innervation of the canine and human ventricular conducting system Circulation 50 948 19 4
19. Baba N Leighton R. F and Weissler A M Experimental cardiac ischemia Lab Invest 23 168 19/0
20. Corr P B., Pearle [illegible] L. Hinton J R., et al Site of myocardial infarction A determinant of the cardiovascular changes induced by coronary occlusion Manuscript submitted for publication
21. James, T N Anatomy of the coronary arteries, New York, 1961 Hoeber Inc.
22. Oberg B and Thoren P Circulatory responses to stimulation of left ventricular receptors in the cat Acta Physiol Scand 88 8 1973
23. Adgey A A J Mulholland H C., Geddes J S., et al Incidence significance and management of early bradyarrhythmia complicating acute myocardial infarction Lancet 2 1097 1968
24. Abramson, D I Crawford J H and Roberts [illegible] H The coronary blood supply in the cat Anat Rec 58 25 1933

An approach to the treatment of essential hypertension

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In the early phases of essential hypertension, increased cardiac output is the main mechanism of elevated blood pressure but the hemodynamic abnormality in most of the patients with established essential hypertension is an abnormal rise of systemic vascular resistance [1-5] The administration of drugs which have a direct effect on the smooth muscle of the arterial walls seems to be a logical approach to the treatment of such hypertension In hypertensive subjects with intact cardiovascular reflexes however the antihypertensive effect of such a drug is frequently offset by an increase in heart rate and cardiac output [6-14] The blood pressure control with sympatholytic drugs may also be unsatisfactory when the patient is lying down and postural hypotension, weakness and sexual dysfunction are frequently encountered [15-17]

Propranolol the most commonly used beta adrenergic blocking agent, in oral doses of 80 to 160 mg per day has only a mild antihypertensive action,[18-2] whereas the administration of larger doses over long periods of time may have deleterious effects on left ventricular function and still frequently controls blood pressure inadequately in patients with severe hypertension [23, 24] Furthermore, transient hypertensive episodes have been observed during office visits in patients treated by propranolol alone,[22] due probably to unopposed alpha adrenergic receptor-mediated vasoconstriction [3, 27] It seems, therefore reasonable that both beta and alpha adrenergic blockade might be expected to be more effective in lowering blood pressure

In a recent study Majid and associates[21] administering oxprenolol and phentolamine to 12 severe hypertensive patients attained a reduction in blood pressure to normal levels in all subjects The unsatisfactory results reported by Beilin and Juel Jensen[29] with propranolol and phenoxybenzamine are probably explicable by their use of a fixed dose regimen in patients with mainly mild hypertension

The present study was designed to examine the efficacy and side effects of the combined administration of propranolol and phenoxybenzamine to 19 patients with moderate and moderately severe hypertension Our results clearly demonstrated that propranolol and phenoxybenzamine given together in individualized doses were very effective in lowering arterial blood pressure with minimal side effects

Material and Methods

From January 1974, to April 1975 23 patients with essential hypertension were enrolled in the clinical trial The study was completed in 19, the remaining four failed to report back to the clinic and were unavailable to follow up Seven of the 19 patients were considered to have moderately severe hypertension with diastolic blood pressure equal to or greater than 120 mm Hg and 12 had moderate hypertension with diastolic blood pressure at 108 or greater in the recumbent position The clinical data of these patients are outlined in Table I Very old subjects and patients with renal or heart failure or accelerated hypertension were excluded as well as patients for whom beta adrenergic blocking agents were contraindicated A complete description of the experimental nature of the study was presented to all patients and written consent obtained Previous antihy

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Table I Clinical data in 19 patients with essential hypertension

Case No.	Age (yr)	Sex	Race	Family history of hypertension	Duration of known hypertension (yr)	ECG (LVH)†	Cardiomegaly‡ in x ray	Eye fundi (KW)§
1	[illegible]	F	PR	+	15	+	+	II
2	56	F	PR	−	15	−	−	[illegible]
3	[illegible]	F	N	+	15	+	+	II
4	[illegible]	F	N	−	10	−	−	I
5	[illegible]	F	PR	+	9	−	−	I
6	[illegible]	M	N	+	15	+	−	II
7	36	F	PR	+	1	−	−	I
8	43	M	W	+	3	+	−	II
9	58	F	N	+	35	−	+	II
10	[illegible]	M	N	+	14	+	+	II
11	[illegible]	F	N	+	3	−	+	I
12	38	M	N	+	4	+	−	I
13	[illegible]	F	N	+	2	−	−	II
14	49	M	PR	+	1	+	+	I
15	51	M	N	+	3	+	−	II
16	[illegible]	M	PR	−	10	−	−	I
17	37	F	N	+	[illegible]	+	+	I
18	51	F	PR	+	5	−	−	II
19	[illegible]	M	PR	+	1	−	−	II

*PR, Puerto Rican N Negro W white
†LVH, left ventricular hypertrophy
‡Cardiothoracic ratio greater than 55 per cent.
§KW Keith Wagner Barker classification

pertensive therapy was discontinued for 1 to 3 weeks prior to the drug administration None of these patients was on guanethidine or reserpine therapy During this period blood pressure pulse rate and body weight were measured once or twice and complete descriptions of any symptoms or complaints were recorded Routine studies consisted of physical examination and laboratory procedures, including electrocardiogram chest x ray rapid sequence intravenous pyelogram complete blood count routine urinalysis multichannel automated blood chemistries and urinary catecholamine metabolite test Changes in the ocular fundi were graded to the Keith Wagner scale For left ventricular hypertrophy in the electrocardiogram the Romhilt and Estes scoring system was used

The standard cuff with the mercurial sphygmomanometer was used to measure blood pressure from the right arm recording the beginning of Korotkoff sounds and their muffling for the systolic and diastolic blood pressures respectively Blood pressure was recorded while in the recumbent position for 10 minutes and in the erect position for 3 minutes Three recordings in each position were averaged for the calculations

After completion of the control period propranolol (Inderal) in a dose of 20 mg by mouth four times a day as the sole antihypertensive therapy was started in 10 patients and the propranolol together with phenoxybenzamine (Dibenzyline) was started in 9 cases Propranolol was titrated against heart rate and blood pressure response up to a maximal amount of 160 mg a day One patient received 80 mg and 5 patients received 120 mg because of severe sinus bradycardia (pulse rate less than 52 beats per minute in the recumbent position) while on a higher dose Finally all 19 patients received both propranolol and phenoxybenzamine Phenoxybenzamine was started at 10 to 20 mg per day and the dosage was increased by 10 to 20 mg increments at each visit (2 week intervals) up to a level determined by the patient s ability to tolerate the drug the maximal dosage being 50 mg a day divided into two to four doses If the blood pressure decreased to normal levels in both positions (140/90 mm Hg or less) a smaller amount of phenoxybenzamine was prescribed In one of the above [illegible] patients started on

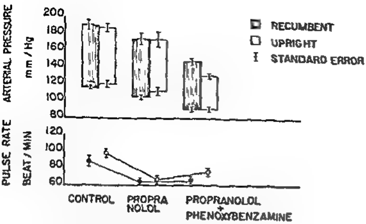

Fig 1 Mean blood pressure and pulse rate in 10 hypertensive subjects in the control period during propranolol and propranolol with phenoxybenzamine administration

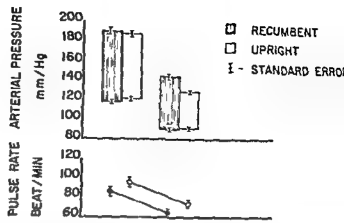

Fig 2 Mean blood pressure and pulse rate in 19 hypertensive subjects including the 10 in Fig 1 in the control period and during propranolol with phenoxybenzamine administration

propranolol alone, the drug was increased up to a maximal amount of 160 mg per day then phenoxybenzamine was administered alone up to a maximal dose 20 mg for 4 weeks and finally propranolol was added to phenoxybenzamine at a daily dosage of 160 mg

At every clinic visit complete physical examination was carried out and blood pressure and pulse rate in both positions were recorded Body weight was also measured and the patients were asked for complaints in general and specifically for the following Weakness drowsiness, sexual function, shortness of breath dizziness, stuffiness of the nose, dryness of the mouth, and depression At the end of the drug therapy period routine testing was repeated

For statistical analysis the t test for paired data was used

Propranolol

The effect on blood pressure and pulse rate of orally administered propranolol over a period ranging from 4 to 12 weeks (10 patients) is presented in Fig 1 In the recumbent position mean systolic blood pressure decreased from 191 to 175 mm Hg ($p < 0\,005$) and mean diastolic pressure from 116 to 105 ($p < 0\,001$) during the control and propranolol periods, respectively In the upright position mean systolic and mean diastolic blood pressure decreased from 188 and 121 to 174 (ns) and 112 ($p < 0\,005$) respectively Normal blood pressure was not attained in any of the patients Pulse rate decreased significantly in both positions ($p < 0\,001$) and three patients developed sinus bradycardia (pulse rate less than 60 beats per minute) Body weight increased slightly but not significantly

Propranolol and phenoxybenzamine

Effect on blood pressure The addition of 20 to 50 mg of phenoxybenzamine to propranolol in 10 patients (Fig I) produced a substantial reduction in systolic and diastolic blood pressure in both positions Thus, in the recumbent position mean systolic blood pressure decreased from 175, during propranolol therapy to 148 ($p < 0\,001$) during propranolol and phenoxybenzamine administration and mean diastolic arterial pressure decreased from 105 to 91 ($p < 0\,001$) In the upright position mean systolic blood pressure decreased during propranolol and phenoxybenzamine therapy from 174 to 131 ($p < 0\,001$) and mean diastolic arterial pressure from 112 to 91 ($p < 0\,001$) during the combined therapy

In Table II and Fig 2 the effect of combined administration of propranolol and phenoxybenzamine on blood pressure in nine patients together with the 10 patients reported above (19 in all) is presented There was a significant ($p < 0\,001$) reduction in both systolic and diastolic blood pressure in both positions during combined therapy Normal blood pressure (140/90 or less) or near normal (150/100 or less) was attained in 14 patients in the recumbent and in 17 patients in the upright position Orthostatic hypotension was not observed

Effect on pulse rate and body weight The addition of phenoxybenzamine to propranolol in 10 patients (Fig 1) produced a slight increase in pulse rate which became significant only in the upright position ($p < 0\,02$) In the whole group of 19 patients (Table III) pulse rate during the combined administration of propranolol and phenoxybenzamine decreased significantly in both positions ($p < 0\,001$), and sinus bradycardia

Table II Effect of combined administration of propranolol and phenoxybenzamine on blood pressure in 19 patients with essential hypertension

Case No.	Control period				Propranolol and phenoxybenzamine				Daily dosage of	
	Recumbent		Upright		Recumbent		Upright		Propranolol (mg)	Phenoxybenzamine (mg)
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic		
1	155	117	190	124	148	88	130	95	160	30
2	160	108	170	125	128	88	126	[illegible]	160	40
3	190	120	174	115	144	96	125	88	160	30
4	190	110	190	110	130	88	128	96	160	20
5	190	108	192	114	158	[illegible]	128	[illegible]	160	20
6	218	130	218	146	[illegible]	98	138	100	160	[illegible]
	200	110	200	122	135	80	128	88	160	40
8	210	138	[illegible]	130	150	100	134	[illegible]	160	50
9	225	130	215	[illegible]	165	90	122	80	80	40
10	190	125	[illegible]	128	155	[illegible]	138	102	160	[illegible]
11	180	108	180	[illegible]	[illegible]	82	122	84	160	[illegible]
12	[illegible]	114	180	120	140	82	148	102	120	40
13	200	118	[illegible]	106	165	88	150	[illegible]	160	40
14	188	124	192	[illegible]	140	90	128	90	160	50
15	190	112	196	120	140	90	120	88	160	40
16	[illegible]	118	[illegible]	122	135	90	[illegible]	[illegible]	120	30
17	208	130	208	134	140	90	[illegible]	88	120	20
18	180	110	180	110	130	84	128	[illegible]	120	30
19	[illegible]	115	160	110	122	90	120	95	[illegible]	30
Mean	190	118.2	188	121.3	144	90	[illegible]	91	145	36
S.E.	±4.2	±2.1	[illegible]	±2.2	±3.1	±1.7	[illegible]	±1.7	±5.8	±2.1

S.E. = standard error
$p < 0.001$

was observed in four patients Propranolol was given to six patients in dosage of 80 to 120 mg a day to combat severe sinus bradycardia (fewer than 52 beats per minute) while on higher doses.

During the combined therapy in the whole group of 19 patients body weight increased initially significantly ($p < 0.01$) but at the end of 3 to 10 weeks of therapy body weight remained unchanged.

Side effects By titrating the dosage of both drugs against heart rate and blood pressure responses no serious side effects were observed Orthostatic hypotension was not encountered In three male patients there was a partial inhibition of ejaculation There was no subjective evidence of heart failure and there was no other side effect such as has been described in some patients receiving phenoxybenzamine alone

Discussion

Beta adrenergic blocking agents Beta adrenergic blockade has been advanced in the treatment of hypertension for many years [31,3] Although the dose of propranolol required to produce beta blockade is often less than the dose required for control of blood pressure its antihypertensive effect is at least partly related to its beta adrenergic blocking activity [3] Initial studies of hypertensive subjects suggested that blood pressure reduction with propranolol therapy was correlated with the level of pretreatment cardiac output [2] However this has been disputed by recent hemodynamic studies [20] Although cardiac output is decreased to the same degree by acute intravenous[16] and chronic oral administration of propranolol [2] blood pressure is reduced only with chronic administration [22] due probably to adaptation of the peripheral circulation [20] Other possible mechanisms related to the antihypertensive effect of propranolol are its antirenin activity [20] an effect on the central nervous system [4] a baroreceptor effect [3] and an effect of its metabolites [1]

The hypotensive response to beta blockade alone has been variable Some investigators have found that propranolol is a very effective and safe treatment for essential hypertension [3, 34] whereas others have found that propranolol produced a significant reduction in blood pressure in only a

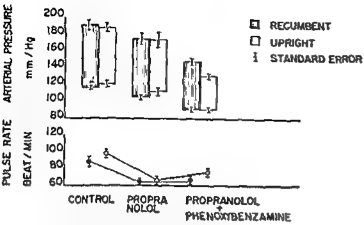

Fig 1 Mean blood pressure and pulse rate in 10 hypertensive subjects in the control period during propranolol and propranolol with phenoxybenzamine administration

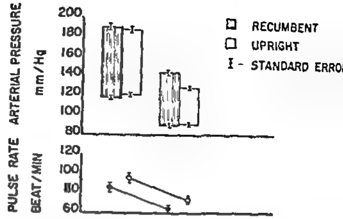

Fig 2 Mean blood pressure and pulse rate in 19 hypertensive subjects including the 10 in Fig 1 in the control period and during propranolol with phenoxybenzamine administration

propranolol alone, the drug was increased up to a maximal amount of 160 mg per day, then phenoxybenzamine was administered alone up to a maximal dose 20 mg for 4 weeks and finally propranolol was added to phenoxybenzamine at a daily dosage of 160 mg

At every clinic visit complete physical examination was carried out and blood pressure and pulse rate in both positions were recorded Body weight was also measured and the patients were asked for complaints in general and specifically for the following Weakness, drowsiness sexual function shortness of breath dizziness, stuffiness of the nose dryness of the mouth and depression At the end of the drug therapy period, routine testing was repeated

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Propranolol and phenoxybenzamine

Effect on blood pressure The addition of 20 to 50 mg of phenoxybenzamine to propranolol in 10 patients (Fig 1) produced a substantial reduction in systolic and diastolic blood pressure in both positions Thus in the recumbent position mean systolic blood pressure decreased from 175, during propranolol therapy to 148 ($p < 0.001$), during propranolol and phenoxybenzamine administration, and mean diastolic arterial pressure decreased from 105 to 91 ($p < 0.001$) In the upright position mean systolic blood pressure decreased during propranolol and phenoxybenzamine therapy from 174 to 131 ($p < 0.001$) and mean diastolic arterial pressure from 112 to 91 ($p < 0.001$) during the combined therapy

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Table II Effect of combined administration of propranolol and phenoxybenzamine on blood pressure in 19 patients with essential hypertension

Case No.	*Control period*				*Propranolol and phenoxybenzamine*				*Daily dosage of*	
	Recumbent		*Upright*		*Recumbent*		*Upright*			
	Systolic	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Propranolol (mg)*	*Phenoxybenzamine (mg)*
1	185	117	190	124	148	88	130	95	160	30
2	160	108	1[illegible]0	125	1[illegible]8	88	126	98	160	40
3	190	120	174	115	144	96	1[illegible]5	88	160	30
4	190	110	190	110	130	88	1[illegible]8	96	160	20
5	1[illegible]0	108	192	114	158	82	128	[illegible]8	160	20
6	218	130	218	146	152	98	138	100	160	[illegible]0
7	[illegible]00	110	[illegible]00	1[illegible]2	135	80	128	88	160	40
8	210	138	202	130	150	100	134	98	160	50
9	225	130	215	128	165	90	122	80	80	40
10	190	1[illegible]5	1[illegible]0	1[illegible]8	155	11[illegible]	138	10[illegible]	160	[illegible]0
11	180	108	180	120	132	82	1[illegible]2	84	160	30
[illegible]	1[illegible]6	114	180	1[illegible]0	140	82	148	102	120	40
13	200	118	1[illegible]8	106	165	88	1[illegible]0	80	160	40
14	188	1[illegible]4	192	120	140	90	128	90	160	[illegible]0
15	190	112	196	1[illegible]0	140	90	120	88	160	40
16	1[illegible]8	118	1[illegible]8	1[illegible]	135	90	120	90	1[illegible]0	30
17	[illegible]08	130	[illegible]08	134	140	90	1[illegible]0	88	1[illegible]0	[illegible]0
18	180	110	180	110	130	84	128	90	1[illegible]0	30
19	150	115	160	110	122	90	1[illegible]0	98	120	30
Mean	190	118.2	188	121.3	144	90	129	91	145	36
S.E.	±4.2	±2.1	±2.9	±2.2	±3.1	±1.[illegible]	±2.0	±1.7	±5.8	±2.1

S.E. = standard error
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was observed in four patients Propranolol was given to six patients in dosage of 80 to 120 mg a day to combat severe sinus bradycardia (fewer than 52 beats per minute) while on higher doses.

During the combined therapy in the whole group of 19 patients body weight increased initially significantly ($p < 0.01$) but at the end of 3 to 10 weeks of therapy body weight remained unchanged

Side effects By titrating the dosage of both drugs against heart rate and blood pressure responses no serious side effects were observed Orthostatic hypotension was not encountered In three male patients there was a partial inhibition of ejaculation There was no subjective evidence of heart failure and there was no other side effect such as has been described in some patients receiving phenoxybenzamine alone

Discussion

Beta adrenergic blocking agents Beta adrenergic blockade has been advanced in the treatment of hypertension for many years [3] Although the dose of propranolol required to produce beta blockade is often less than the dose required for control of blood pressure its antihypertensive effect is at least partly related to its beta adrenergic blocking activity [3] Initial studies of hypertensive subjects suggested that blood pressure reduction with propranolol therapy was correlated with the level of pretreatment cardiac output [33] However this has been disputed by recent hemodynamic studies [22] Although cardiac output is decreased to the same degree by acute intravenous[36] and chronic oral administration of propranolol [3] blood pressure is reduced only with chronic administration [22] due probably to adaptation of the peripheral circulation [22] Other possible mechanisms related to the antihypertensive effect of propranolol are its antirenin activity [39] an effect on the central nervous system [40] a baroreceptor effect [31] and an effect of its metabolites

The hypotensive response to beta blockade alone has been variable Some investigators have found that propranolol is a very effective and safe treatment for essential hypertension [31,3] whereas others have found that propranolol produced a significant reduction in blood pressure in only a

Table III Effect of combined therapy with propranolol and phenoxybenzamine on pulse rate and bod weight in 19 hypertensive subjects

Case No	Control period			Propranolol and phenoxybenzamine				
	Pulse rate (beat/min)		Weight (kg)	Pulse rate (beat/min)		Weight after 2 wk	Weight at end	Duration of combined therapy (wk
	Recumbent	Upright		Recumbent	Upright			
1	86	[illegible]	71 8	64	80	72 3	71 8	7
2	96	100	71 4	60	72	72 3	72 7	9
3	72	92	73 2	54	76	75 5	74	5
4	88	104	45 7	84	88	47 3	48 2	7
5	112	116	56 4	70	76	56 4	[illegible]	10
[illegible]	100	112	73	56	76	73	73 2	4
7	70	82	91 5	62	68	97 3	95 2	4
8	[illegible]	96	65 7	68	76	65 9	65 9	5
9	[illegible]	76	84 6	54	70	86 4	85 7	6
10	72	88	72	72	100	71 8	72 3	6
11	84	88	82 3	68	68	83 6	82 3	4 5
12	70	78	92 3	60	66	93 2	92 7	5
13	88	100	62 7	68	72	63 8	62 7	6
14	80	92	82 7	60	84	84 5	82	4
15	92	98	88 2	70	74	88 2	86 8	3
16	90	92	83 2	68	80	82 7	82 3	4
17	88	90	76 4	68	72	76 4	76 4	4
18	96	100	83 3	62	64	90 9	83 9	[illegible]
19	88	100	73 6	54	60	73 6	73 4	4
Mean	86	95	75 5	64	[illegible]	76 5	[illegible]	[illegible]
S E	±2 6	±2 4	±2 7	±1 7	±2 1	±2 9	2 7	± 0 4

S E = standard error
Significant at $P < 0.01$ and < 0.001 respectively

small number of cases[20-22] In our series a clinically satisfactory reduction in blood pressure was not attained in any patient despite the significant decrease of mean blood pressure

Combined beta and alpha adrenergic blockade Alpha adrenergic receptor blocking drugs phentolamine (Regitine) and phenoxybenzamine (Dibenzyline), have been used in the treatment of hypertension due to pheochromocytoma,[42] in peripheral vascular disease in shock[44, 45] in severe congestive heart failure[46] and in glaucoma[47] Phenoxybenzamine alone or in combination with propranolol has also been used in the treatment of essential hypertension Haimovici and associates[48] administered phenoxybenzamine alone to 27 uncomplicated essential and malignant hypertensive patients and attained a significant decrease in both supine and standing blood pressure with symptomatic improvement in 75 per cent of the cases However, dryness of the mouth and stuffiness of the nose were not infrequent side effects, whereas drowsiness and fatigue occurred in a few patients Dizziness and palpitations were also observed in several cases, but most of the side effects were observed during the first few days of treatment and with proper adjustment of the dosage the patients showed few of the above symptoms

In the present study propranolol at a dose of 80 to 160 mg and phenoxybenzamine at a dose of 20 to 50 mg a day produced a highly significant reduction in both systolic and diastolic blood pressure in both positions Clinically satisfactory levels (140/90 mm Hg or less) were reached in 10 patients whereas diastolic blood pressure of 100 mm Hg or less was attained in 18 patients in the recumbent and in 17 patients in the upright position Orthostatic hypotension was not observed in any of the patients The only encountered side effect was a reduction in ejaculation in 50 per cent of the male patients Fluid retention was observed in most of the patients during the first 2 weeks of the therapy but at the end of the present study mean body weight had not changed significantly

Blockage of beta adrenergic receptors alone may result in vasoconstriction of the renal vessels, due to the unmasking of catecholamine effects on alpha receptors and a decrease in renal blood flow during propranolol administration has

been reported Both alpha and beta adrenergic receptors are important in the regulation of the circulation through the kidney and the therapy of hypertension with drugs that block the vasoconstrictive effect of alpha receptors may retard the progression of renal vascular disease and prevent kidney damage which is a major cause of death in hypertension[30] In acute experiments phenoxybenzamine produces plasma volume expansion and a fall in the central venous pressure[31] as the result of differential effects on precapillary and postcapillary resistance vessels and a greater inhibition of sympathetic vasoconstriction in the systemic than in the pulmonary vascular bed[32] In normovolemic subjects at rest renal blood flow is not altered remarkably during phenoxybenzamine administration [illegible] but in the presence of increased adrenergic vasoconstriction renal blood flow may increase producing an increase in urinary output[4, 32]

Tachyphylaxis to phenoxybenzamine when administered alone over a long period has been reported[4] but was not noticed during the 3 to 10 weeks of combined administration of propranolol and phenoxybenzamine in the present study

In a recent study Majid and associates[29] administered oxprenolol and phentolamine to 12 severely hypertensive patients and attained a reduction in blood pressure to normal levels in all subjects without any side effects or orthostatic hypotension Also body fluid retention was not observed and tolerance was not encountered in six patients followed for 6 months. However Beilin and Juel-Jensen[29] reported a high incidence of side effects produced by the administration of propranolol and phenoxybenzamine in nine patients over a [illegible] week period The unsatisfactory results in that study may be due to the fact that they used a fixed-dosage regimen in patients with mild hypertension

Phenoxybenzamine does not block the sympathetic reflexes and the blood pressure reduction is accompanied by an increase in heart rate[4, 32, 5] These hemodynamic changes were noticed in one patient in the present study to whom phenoxybenzamine was administered alone The addition of propranolol reduced heart rate and decreased blood pressure still further in this patient

Phenoxybenzamine as the sole antihypertensive agent has never found popularity in the treatment of essential hypertension probably because in patients with intact reflexes it increased heart rate and cardiac output which offset its antihypertensive effect The addition of a beta adrenergic receptor blocking agent is a logical approach to prevent tachycardia and heighten the antihypertensive action The present trial clearly demonstrates that the combined administration of propranolol and phenoxybenzamine in individualized doses lowered blood pressure to normal or nearly normal levels in 89 per cent of patients with moderate and moderately severe essential hypertension Except for decrease in ejaculation in some male patients no other side effect was observed during the 3 to 10 weeks of therapy The follow up results in eight patients over a [illegible] to 8 month period have also indicated that the combined administration of alpha and beta adrenergic receptor blocking agents produces a significant and consistent reduction in blood pressure with minimal side effects.

Summary

The efficacy and side effects of the combined administration of propranolol and phenoxybenzamine were examined in 19 patients with moderate and moderately severe essential hypertension By titrating the dosage of both drugs against pulse rate and blood pressure response propranolol was given between 80 and 160 mg and phenoxybenzamine between 20 and 50 mg per day in divided doses There was a substantial reduction in both systolic and diastolic blood pressure in both recumbent and upright positions without orthostatic hypotension Normal blood pressure (140/90 mm Hg or less) or near normal (150/100 mm Hg or less) was attained in 14 of the patients in the recumbent and 17 in the upright position Pulse rate also decreased significantly whereas body weight increased but not significantly so Except for a reduction of ejaculation in three out of six male subjects no symptomatic side effects were detected and no changes in the liver or renal function or in blood count were observed. Despite the short duration of therapy 3 to 10 weeks, this study clearly demonstrates that propranolol and phenoxybenzamine given together in individualized doses are very effective in lowering arterial blood pressure with minimal side effects

The authors are grateful to Dr Robert C Hoppe Director of Clinical Services, Smith Kline and French Laboratories, Philadelphia, Pa for the generous supply of phenoxybenzamine and Dr William Abrams Director Ayerst Laboratories New York, N Y., for propranolol.

REFERENCES

1 Lund-Johansen P Hemodynamics in early essential hypertension Acta Med Scand 181 (Suppl 482) 1 1967
2 Eich R H Cuddy R P Smulyan H and Lyons R H Hemodynamics in labile hypertension A follow up study Circulation 34 299 1966
3 Frohlich E D Tarazi R C and Dustan H P Reexamination of the hemodynamics of hypertension Am J Med Sci 257 9 1969
4 Bello C T Sevy R W and Harakal C Varying hemodynamic patterns in essential hypertension Am J Med Sci 250 58 1965
5 Finkielman S Worcel M and Agrest A Hemodynamic pattern in essential hypertension Circulation 31 356 1965
6 Ablad B A study of the mechanism of the hemodynamic effects of hyrdalazine in man Acta Pharmacol (Kbh) 20 (Suppl 1) 1 1963
7 Gilmore E Weil J and Chidsey C Treatment of essential hypertension with a new vasodilator in combination with beta adrenergic blockade N Engl J Med 282 521 1970
8 Zacest R Gilmore E and Koch Weser J Treatment of essential hypertension with combined vasodilation and beta adrenergic blockade N Engl J Med 286 617 1972
9 Gottlieb T B Katz F H and Chidsey C A III Combined therapy with vasodilator drugs and beta adrenergic blockade in hypertension A comparative study of minoxidil and hydralazine Circulation 45 571 1972
10 Rubin A A Zitowitz L and Hausler L Acute circulatory effects of diazoxide and sodium nitrite J Pharmacol Exp Ther 140 46 1963
11 Finnerty F A Jr Kakaviatos N Tuckman J et al Clinical evaluation of diazoxide A new treatment for acute hypertension Circulation 28 203 1963
12 Hammer J Ulrych M and Freis E D Hemodynamic and therapeutic effects of guancydine in hypertension Clin Pharmacol Ther 12 78 1971
13 Russo C Mendlowitz M Gitlow S E Wolf R L Bertani L M and Rocaceanu S Antihypertensive effect of guancydine in hypertensive patients Clin Pharmacol Ther 13 875 1972
14 DeGuia D Mendlowitz M Russo C Vlachakis N D and Antram S The effect of trimazosin in essential hypertension Curr Ther Res 15 339 1973
15 Fertig H Fletcher L Jr Schvatz N et al Clinical experiences with guanethidine in ambulatory hypertensive subjects N Engl J Med 265 268 1961
16 Prichard B N C Johnston A W Hill I D et al Bethanidine guanethidine and methyldopa in treatment of hypertension A within patient comparison Br Med J 1 135 1968
17 Horwitz D Pettinger W A Orvis H et al Effects of methyldopa in fifty hypertensive patients Clin Pharmacol Ther 8 224 1967
18 Paterson J W and Dollery C T Effects of propranolol in mild hypertension Lancet 2 1148 1966
19 Waal H J Hypotensive action of propranolol Clin Pharmacol Ther 7 588 1966
20 Nicotero J A Beamer V Moutsos S E and Shapiro A P Effects of propranolol on the pressor responses to noxious stimuli in hypertensive patients Am J Cardiol 22 657 1968
21 DeGuia D Mendlowitz M and Vlachakis N D Effect of propranolol on cardiovascular reactivity to epinephrine (E) and norepinephrine (NE) in labile essential hypertension (abst) Clin Res 22 271A 1974
22 Tarazi R C and Dustan H P Beta adrenergic blockade in hypertension Practical and theoretical implications of long term hemodynamic variations Am J Cardiol 29 633 1972
23 Majid P A Sharma B Saxton C Stoker J B and Taylor S H Haemodynamic effects of oxprenolol in hypertensive patients Postgrad Med J 46 (Nov suppl) 67 1970
24 Greenblatt D J and Koch weser J Adverse reactions to propranolol in hospitalized medical patients A report from the Boston collaborative drug surveillance program AM HEART J 86 478 1973
25 Youmans, P L Green H D and Denison A B Jr Nature of the vasodilator and vasoconstrictor in skeletal muscle of the dog Circ Res 3 171 1955
26 De La Lande I S and Whelan R F The effect of antagonists on the response of the forearm vessels to adrenaline J Physiol 148 548 1959
27 Assaykeen T A Clayton P L Goldfien A and Ganong W F Effect of alpha and beta adrenergic blocking agents on the renin response to hypoglycemia and epinephrine in dogs, Endocrinology 87 1318 1970
28 Majid P A Meeran M K Benaim M E Sharma B and Taylor S H Alpha and beta adrenergic receptor blockade in the treatment of hypertension Br Heart J 36 588 1974
29 Beilin L J and Juel-Jensen B E Alpha and beta adrenergic blockade in hypertension Lancet 1 979 1972
30 Romhilt D W and Estes E H Jr A point score system for the ECG diagnosis of left ventricular hypertrophy AM HEART J 75 752 1968
31 Prichard B N C and Gillam P M C Use of propranolol in treatment of hypertension Br Med J 2 725 1964
32 Prichard B N C Propranolol as an antihypertensive agent AM HEART J 79 128 1970
33 Dorph S and Binder C Evaluation of the hypotensive effect of beta adrenergic blockade in hypertension Acta Med Scand 185 443 1969
34 Zacharias, F J and Cowen K J Controlled trial of propranolol in hypertension Br Med J 1 471 1970
35 Kincaid Smith P Management of severe hypertension Am J Cardiol 32 575 1973
36 Ulrych M Frohlich E D Dustan H P and Page I H Immediate hemodynamic effects of beta adrenergic blockade with propranolol in normotensive and hypertensive man Circulation 37 411 1968
37 Prichard B N C Shinebourne E Fleming J and Hamer J Hemodynamic studies in hypertensive patients on oral propranolol Br Heart J 32 236 1970
38 Bayliss W M On the local reactions of the arterial wall to changes in internal pressure J Physiol (Lond) 28 220 1902
39 Buehler F R Laragh J H Vaughan E D Jr Brunner H R Gavras H and Baer L The antihypertensive action of propranolol Specific antirenin responses in high and normal renin forms of essential renal, renovascular and malignant hypertension in Laragh J H editor Hypertension manual New York Yorke Medical Books Dun Donnelley Publishing Co p 873 1975
40 Kelliher G J and Buckley J P Central hypotensive activity of dl and d propranolol J Pharm Sci 59 1276, 1970
41 Hansson L Olander R and Aberg H Twice daily propranolol treatment for hypertension Lancet 2 713 1971
42 Bannon W G and Allen E V The effect of adrenolytic drugs on pheochromocytoma with functioning

metastatic lesions Report of case Proc. Staff Meet Mayo Clin. [illegible] 459 1952.

43. Friend, D [illegible] and Edwards, E A. Use of Dibenzyline as a vasodilator in patients with severe digital ischemia Arch. Intern. Med. 93 928 1954

44. Wilson, R. F Jablonski, [illegible] V and Thal A P The usage of Dibenzyline in clinical shock Surgery 56 172, 1964.

45. Nickerson, M., and Gourzis, J T Blockade of sympathetic vasoconstriction in the treatment of shock J Trauma 2.399 1962.

46. Majid, P A., Sharma, B., and Taylor [illegible] H Phentolamine for vasodilator treatment of severe heart failure Lancet 2.719 1971

47. Primrose J Dibenzyline in glaucoma Br J Ophthalmol. 39 307 1955

48. Haimovici, H., Moser [illegible] and Krakauer [illegible] Effect of oral 688A on blood pressure in normotensive and hypertensive subjects, Proc. Soc. Exp Biol Med 77 477 1951

49. Ibsen, H., and Sederberg Olsen [illegible] Changes in glomerular filtration rate during long term treatment with propranolol in patients with arterial hypertension Clin Sci. 44 129 1973.

50. Smirk, H and Hodge J V Causes of death in treated hypertensive patients Based on 82 deaths during 1959-61 among an average hypertensive population at risk of 518 persons, Br Med. J 2 1221 1963

51. Skillman, J J., Lyons, J H Zollinger R. M., Jr Eltringham, M B and Moore F [illegible] Physiologic effects of phenoxybenzamine infusion in man Surg. Forum 17 50 1966.

52. Nickerson, M., and Hollenberg, [illegible] K Blockade of α adrenergic receptors, in Root, W S., and Hofmann [illegible] C editors [illegible]hysiological pharmacology Vol. 4 The nervous system, Part [illegible] Autonomic nervous system drugs, New York 1967 Academic Press, Inc., pp 356-370

53. Moran N C and Perkins, M E An evaluation of adrenergic blockade of the mammalian heart, J Pharmacol. Exp. Ther 133 192 1961

Computer simulation of the precordial QRS complex. Effects of simulated changes in ventricular wall thickness and volume

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During the past five decades investigators have utilized two general approaches to study the relationship between the electrical potentials generated by the heart and the physiologic condition of the heart. The classical approach is to compare the electrocardiogram (ECG) obtained in an individual to some independent measurements of the heart in that patient. Such independent measurements can be obtained either in vivo[1,2] or post mortem.[3-6] The second basic approach utilizes models[7-15] and describes the heart as a current generator and the torso as a finite or infinite volume conductor. These models in turn utilize either an inverse or a forward approach to the problem. The inverse approach measures the potential on the body surface and uses the information to calculate the distributed electrical forces in the heart (surface potential → cardiac generator). Investigators using the forward approach (cardiac generator → surface potential) construct models of the cardiac generator with either a limited number of multipoles[7,8] or a large number of dipoles.[9-14] The model described here utilizes 1,500 dipoles and the output is presented as a standard precordial ECG.

This model is unique because it permits the investigator to vary specific parameters (cardiac shape, wall thickness, activation sequence, and velocity of depolarization) and observe their effects on the precordial QRS complex. In this study the effects of changing left ventricular volume and left ventricular wall thickness on the precordial QRS complexes generated by the model were examined in detail.

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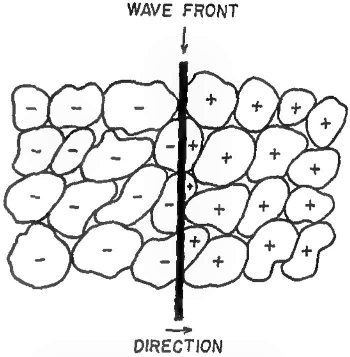

Fig. 1. Schematic illustration of depolarization of a small section of muscle. (−) sign denotes depolarized cells where the membrane is a layer of dipoles whose negative poles are outside the cell. (+) sign denotes polarized cells.

Methods

Since individual cardiac cells act electrically as dipole layers, the model uses the dipole layer concept to simulate the contribution of various groups of cardiac cells to the total electrical potential of the myocardium (Fig. 1). Cells which

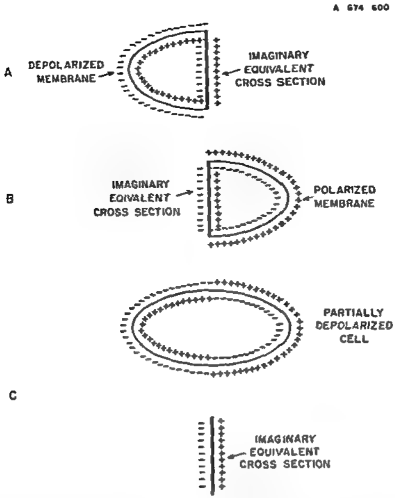

Fig 2 The equivalent cross section of a partially depolarized cell (*A*) The equivalent of the depolarized portion (*B*) The equivalent of the polarized portion (C) The imaginary equivalent of the entire cell.

are either fully depolarized or fully repolarized do not contribute to the potential because the poten tial created by a closed layer of homogeneously distributed dipoles is zero anywhere outside this layer Thus only the partially depolarized cells affect this potential (This assumes that repolari zation of any ventricular cell does not occur until after both ventricles have been depolarized This assumption is reasonable since depolarization of a single cell takes 1 msec and thereafter there is a 200 msec plateau prior to repolarization if an injury potential or a major conduction defect is not present [1])

The solid angle concept is utilized to calculate the potential of partially depolarized cells The potential created at a point p by a layer of dipoles whose surface density is μ is equal to $\Omega\mu$, where Ω is the solid angle in which p sees the layer An imaginary dipole layer is substituted for each partially depolarized cell and the entire muscle mass is represented by a wave front of uniformly distributed dipoles (Fig 2) The exact value of the density of these dipoles which is partially depen dent on intracellular and extracellular conductiv ity is not taken into consideration Furthermore the ratio of the cross sectional area of the cells to the cross sectional area of the tissue is assumed to be independent of the orientation of the wave front relative to the axis of the fibers Also the torso is assumed to be homogeneous and infinite As a consequence of these assumptions the voltage in the calculated precordial ECG s is presented in arbitrary rather than absolute units The wave front of the dipoles has an estimated width of 1 mm but this model assumes that the width of the wave front is zero

The net effect of the wave front at any time can be estimated from the depolarized portion of the

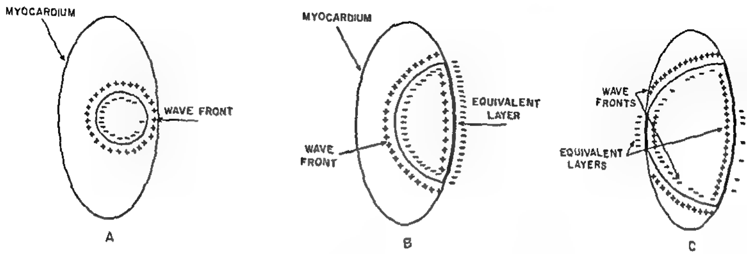

Fig 3 Propagation of the depolarization wave in the ventricles (see text for explanation)

endocardial and epicardial surface at that time This is done in the following manner If no portion of the wave front extends to the endocardial or epicardial surface, the wave front forms a closed shell of dipoles and therefore generates a zero potential (Fig 3, *A*) When any portion of the wave front reaches the epicardial and/or the endocardial surface, the solid angle concept can be utilized on a macroscopic scale to substitute the wave front within the muscle with an equivalent dipole layer (imaginary wave front) at the endocardial and epicardial surfaces of the ventricular walls (Fig 3, *B* and *C*) These imaginary wave fronts cover the depolarized portion of the ventricular walls Thus, the sequence of activation of the walls conveys the information for calculating the precordial ECG

Propagation of the wave front is simulated in the following manner A set of activation points is located in the endocardium An imaginary wave front spreads from each activation center starting at the moment at which the center has been activated by the conduction system of the ventricles In accordance with Huygen s principle,[18] the real wave front is an envelope of these progressively spreading imaginary wave fronts In time, larger and larger portions of the ventricular walls are crossed by these spreading wave fronts and eventually the entire heart is depolarized The activation wave was assumed to be unvarying in amplitude In addition, the transmural propagation velocity was assumed to be unvarying Although studies in the dog suggest that there is significant variation in transmural velocity,[19] this variation in transmural velocity is probably not present in man [6]

The configuration of the ventricles was simplified (Figs 4*A* and 4*B*) and divided into 18 separate parallel slices The cross sectional shape of the left ventricle was circular and the right ventricular free wall was a portion of an ellipse (Fig 4*A*) The ratio of the internal long axis of the left ventricle to the minor axis taken at the midportion of the left ventricle was approximately 2 1 (Fig 4*B*) The shape of the right ventricle assumed by the model is shown in Figs 4*A* and 4*B* Under control conditions the left ventricular wall thickness was assumed to be 1 cm and the right ventricular wall thickness was assumed to be 3 mm Each cross section contained a variable number of trapezoidal elements which formed the epicardial and endocardial surfaces of each slice (Fig 4*A*) The total number of these elements in both ventricles was 1 500 A dipole whose magnitude is proportional to the area of each trapezoid is attached perpendicularly to it This dipole is turned on when passed by the depolarization wave front and remains on until the end of the activation sequence The value of the precordial ECG at every moment is calculated by means of the solid angle technique by taking into account contributions from only the turned on dipoles

Each cross section had approximately five activation centers (total number in both ventricles was 90) distributed on the endocardial surface The sequence of activation was based on the

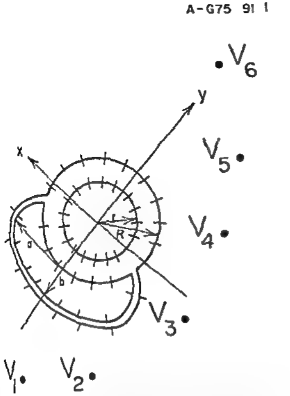

Fig 4A. The cross section shown is taken from the fourth level from the Y coordinate line of Fig 4B a and b are the radii of the ellipse (equation A.2 in the Appendix) and r and R are the inner and outer radii of the circles (equation A 10 in the Appendix) The epicardial and endocardial walls are divided into multiple small trapezoids the vertices of which are shown above

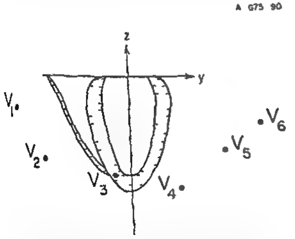

Fig 4B The longitudinal section of the ventricles is shown taken along the long axis of the left ventricle The ventricles are divided into 18 cross-sections The placement of the electrodes in space can be obtained by utilizing their XYZ coordinates shown in Fig 4A and above

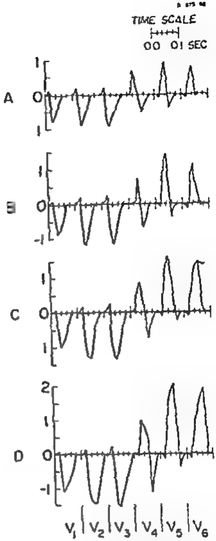

Fig 5 (A) Normal calculated precordial QRS complexes (B D) Effects of increasing left ventricular wall thickness on the calculated precordial QRS complexes (see text for details)

measurements of Durrer and associates [8] This was accomplished in the following manner The cross sections presented by Durrer were idealized so as to conform to the cross sections of our models then the sequence of activation of the endocardial activation centers was set to conform with the sequence described by Durrer and associates In accordance with Durrer's data, the wave front propagation was taken as 40 cm per second in the center of the free wall of the left ventricle and 50 cm per second in the remaining portions of the myocardium The time step was 0 003 second The position in space of the electrodes was obtained by studying detailed anatom

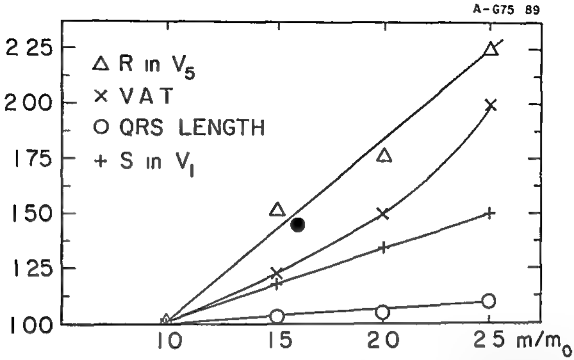

Fig ▮ Relative effects of increasing left ventricular mass on various characteristics of the calculated QRS complexes m/m_0 = calculated mass/control mass The solid circle shows the effects of increasing left ventricular volume 3 × normal on the r wave voltage in V At this volume the m/m increase was 1 6 × control

ical drawings done in several planes[21] The location of the electrodes for which QRS complexes were calculated is shown in Figs *4A* and *4B*

These are the general features of the model The specific formulas utilized are given in the Appendix Also, the manner in which increases in wall thickness and ventricular volume were simulated is detailed in the Appendix

Results

Normal precordial QRS complexes The calculated QRS complexes for leads V_1 to V_6, based upon the model described above, are shown in Fig ▮ *A* The height of the QRS complex is expressed in arbitrary units The configuration of the QRS complexes is very similar to that observed in normal man There is a progressive increase in the R waves and a progressive decrease in the S wave from V_1 to V_6 The Q waves present in Leads V_5 and V_6 are within normal limits The QRS duration is 0 08 second and the ventricular activation time in V_5 is 0 04 second

Effects of progressively increasing left ventricular wall thickness The effects of increasing left ventricular wall thickness from 1 to 2 2 × control on the calculated precordial ECG are shown in Fig 5, *B* to *D* Four characteristics of the QRS complex (R wave voltage in V_5 S wave voltage in V_1 QRS duration and ventricular activation time) increased as the left ventricular thickness parameter was increased in the model

In Fig 6 changes in R wave voltage in V_5 S wave voltage in V_1 QRS duration, and ventricular activation time are shown as a function of increasing left ventricular wall thickness and mass Three of the parameters (R wave voltage in V_5 S wave voltage in V_1, and QRS duration) increase linearly at different rates with increasing left ventricular wall thickness and mass The rate of increase in the ventricular activation time was related in a nonlinear fashion to left ventricular wall thickness Ventricular activation time did not increase markedly until the simulated increase in wall thickness exceeded two times control

Effects of progressively increasing left ventricular volume with constant left ventricular wall thickness The effects of increasing left ventricular volume with constant wall thickness from 0 6 to 3 × control on the calculated precordial QRS complexes are shown in Fig 7 Only R wave voltage in V_5 and QRS duration increased with progressive increases in left ventricular volume

In Fig 8 changes in R wave voltage in V_5 and QRS duration as a function of increasing left ventricular volume and mass are shown At a

comparable increase in left ventricular mass the effects of changes in volume and wall thickness on R wave voltage in V_5 are comparable (Fig 6)

Discussion

The major new observation in this study is that a relatively simple computer model can generate simulated precordial QRS complexes which closely resemble the precordial QRS complexes of man under normal conditions and in the presence of left ventricular hypertrophy

Ideally a model should accomplish three goals (1) It should summarize the existing data that are of critical importance to a given phenomenon in a simple and accurate manner Since the precordial QRS complexes generated by our model closely simulate the normal precordial QRS complexes this suggests that most of the critically important parameters that determine the configuration of the precordial QRS complexes have been incorporated in the model (2) The model should permit the investigator to observe the effects of changing various isolated parameters which may be difficult to manipulate experimentally In our model the manipulation of isolated parameters can be accomplished. Thus the isolated or combined effects of changes in muscle mass ventricular shape and ventricular activation sequence on the calculated QRS complexes can be studied (3) The output of the model should suggest new hypotheses or concepts which may be helpful in understanding the phenomenon being studied and may eventually be testable in either an experimental or a clinical setting Potentially our model may provide basic data to calculate the equivalent dipole generator of the heart or any combination of dipoles or higher multipoles for both normal and pathologic ventricles Furthermore our model could be used to simulate the part of the cardiac generator in a more general model that takes into account the shape of the torso and the conductivities of its various tissues.

In this investigation we utilized the model to examine the effects of changing left ventricular wall thickness and left ventricular volume on the precordial QRS complexes The changes we observed in various characteristics of the QRS complexes will now be discussed and compared with relevant clinical observations

Many clinical studies have shown that the precordial QRS voltage duration and ventricular activation time are increased in patients with left ventricular hypertrophy [3,4] The presence of these abnormalities in the precordial QRS complexes generated by our model suggests that the model may accurately reflect the effects of an increase in ventricular mass on the cardiac generator The model further suggests that the usual ECG characteristics of left ventricular hypertrophy are predominantly related to changes in left ventricular mass as opposed to left ventricular volume A quantitative clinical study[1] in which left ventricular mass and volume were correlated with various ECG features of left ventricular hyper

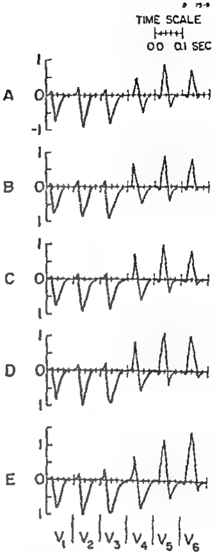

Fig 7 Effects of changing left ventricular volume on the calculated precordial QRS complexes

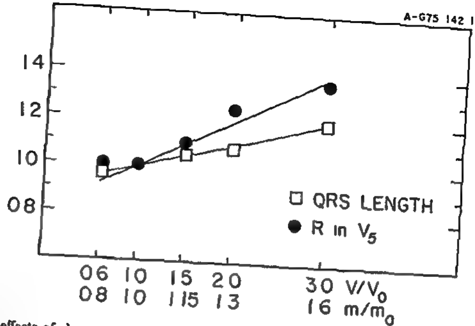

Fig 8 Relative effects of changing ventricular volume on QRS duration and R wave voltage in V V/Vo = simulated volume/control volume m/m_o = simulated mass/control mass

trophy also suggested that ventricular mass is the major determinant of the ECG alterations associated with left ventricular hypertrophy Finally, the model suggests that even under idealized conditions (the torso is homogeneous and infinite and no other cardiac pathology is present) small increases in left ventricular mass are not likely to be detected by the ECG Many clinical studies have shown that the ECG is not a sensitive indicator of left ventricular hypertrophy

In conclusion, we have presented a simple computer model which generates precordial QRS complexes very similar to those observed in normal man Furthermore, simulated increases in left ventricular wall thickness and volume in the model caused changes in the calculated precordial QRS complexes which are characteristic of left ventricular hypertrophy The potential applications of the model are considerable

Summary

The cardiac electric field generated by depolarization of the human ventricle is simulated with a computer model which utilizes 1,500 dipoles The configuration of the ventricles utilized in the model assumed that the cross sectional shape of the left ventricle was circular and the right ventricular free wall was a portion of an ellipse The torso was assumed to be homogeneous and infinite The activation sequence was based on the measurements of Durrer The depolarizational wave was simulated by dipole layers The output of the model is presented as a standard multilead precordial ECG The ECG complexes generated by the model closely resemble the precordial QRS complexes of normal man Simulated increases in wall thickness (1 to 2 2 × control) were associated with changes in the calculated precordial QRS complexes which were characteristic of left ventricular hypertrophy Voltage (R in V_5 or V_6 and S in V_1) and QRS duration increased linearly as a function of calculated left ventricular mass Increases in ventricular activation time were related nonlinearly to changes in left ventricular mass and did not occur in the absence of a simulated increase in wall thickness The effects of simulated changes in left ventricular volume (0 6 to 3 0 × control) on the QRS complex were mainly dependent on the resultant increase in left ventricular mass This model may be useful in simulating the precordial QRS complexes that result from isolated or combined changes in ventricular volume or wall thickness or other disorders of the heart Furthermore, it may be useful whenever a simulation of a QRS generator is needed

We thank Drs Herman L Falsetti and Donald D Brown for reviewing the manuscript and offering many helpful suggestions We also thank Drs Georg Knorr and Francois M Abboud for their encouragement during the course of this investigation

APPENDIX

The formulas and expressions that are utilized in the model are given below The coordinate system was chosen in the following way The z

axis was along the long axis of the left ventricle (Fig 4B) The x and y axes are shown in Fig 4A In this system the circles that form the left ventricle are given by the formula

$$x + y = R \qquad \text{(A 1)}$$

where R is the radius. The ellipses of the right ventricle are given by

$$\frac{x}{a} + \frac{(y-c)}{b} = 1 \qquad \text{(A 2)}$$

where a and b are the radii of the ellipse and c is its center

Each cross section (like Fig 4B) had an inner and an outer circle and an inner and outer ellipse corresponding to the epicardium and the endocardium The vertices of the trapezoids of the left ventricle are given by

$$x = R \cos 2\pi i/N$$
$$y = R \sin 2\pi i/N \qquad i = 1 \quad N \qquad \text{(A 3)}$$

where N is the number of trapezoids per ventricle per cross section (in our case it was 18) and R stands for any inner or outer radius All vertices of the same cross section have of course the same z coordinate

The vertices of the trapezoids of the right ventricle are given by

$$x = D \cos 2\pi i/N \qquad \text{(A 4)}$$

where

$$D = 1/[(\tfrac{1}{a} \cos 2\pi i/N) + (\tfrac{1}{b} \sin 2\pi i/N)]$$

These formulas apply for both inner and outer ellipses Only trapezoids outside the left ventricle are taken into account Let

$$V = (x\ y\ z)\quad V = (x\ y\ z)$$
$$V = (x\ y\ z)\quad V = (x\ y\ z)$$

be the coordinates of the vertices of a trapezoid Let S be the vector defined by the vector product

$$S = ½(V - V) \times (V - V) \qquad \text{(A 5)}$$

then the absolute value |S| of S is the area of the trapezoid and the vector

$$T = S/|S| \qquad \text{(A 6)}$$

is a unit vector perpendicular to the trapezoidal surface

The dipoles were formed as described below The center of the trapezoid where the dipole is located is given by

$$M = \tfrac{1}{4}(V + V + V + V) \qquad \text{(A 7)}$$

This is also the point where a charge of the magnitude S is located A charge of magnitude |S| is located at the point

$$MD = M + \varepsilon T \qquad \text{(A 8)}$$

ε is a small quantity (in our case 0 03 cm) that represents the length of the dipole ε is positive for trapezoids on the *epicardium* and negative for trapezoids on the endocardium The potential created by such a dipole at a point P (where the electrode is located) is given by

$$V = |S| \left(\frac{1}{|M - P|} - \frac{1}{|MD - P|}\right) \qquad \text{(A 9)}$$

As explained in the text the instantaneous value of the QRS at the point P is obtained by adding the contributions (e g A 9) from all the dipoles that are turned on at that instant of time

To increase the wall thickness by a factor F while keeping the volume unchanged the inner radii of the cross sections were not changed The outer radii are given by

$$R_N = r + (R - r)\ F \qquad \text{(A 10)}$$

where R_N is the new outer radius R the normal outer radius and r the normal inner radius

To increase the volume by a factor F while keeping the wall thickness unchanged the new inner radii were given by

$$r = r\ \sqrt{F} \qquad \text{(A 11)}$$

and the new outer radii by

$$R = r + R - r$$

where r_N is the new inner radius

REFERENCES

1 Baxley W A Dodge H T and Sandler H A quantitative angiocardiographic study to left ventricular hypertrophy and the electrocardiogram Circulation **37** 509 1968

2 Hugenholtz P G and Gamboa R Effect of chronically increased ventricular pressure on electrical forces of the heart Circulation 30 511 1964

3 Selzer A Ebnother C L Packard P Stone A. O., and Quinn J E Reliability of electrocardiographic diagnosis of left ventricular hypertrophy Circulation **17** 55 1958

4 Carter W A and Estes E H Electrocardiographic manifestations of ventricular hypertrophy a computer study of ECG anatomic correlations in 319 cases, AM HEART J 68 173 1964

5 Mazzoleni, A Wolff R Wolff L. and Reiner L Correlation between component cardiac weights and electrocardiographic patterns in 185 cases Circulation 30 808 1964

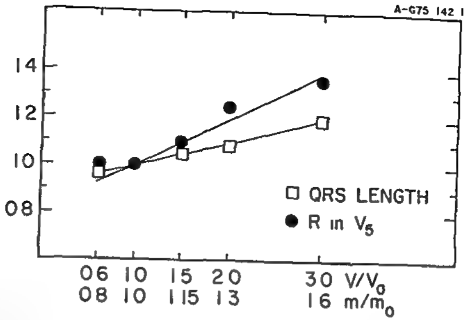

Fig 8 Relative effects of changing ventricular volume on QRS duration and r wave voltage in V V/V_o = simulated volume/control volume m/m_o = simulated mass/control mass

trophy also suggested that ventricular mass is the major determinant of the ECG alterations associated with left ventricular hypertrophy Finally the model suggests that even under idealized conditions (the torso is homogeneous and infinite and no other cardiac pathology is present) small increases in left ventricular mass are not likely to be detected by the ECG Many clinical studies [3 45] have shown that the ECG is not a sensitive indicator of left ventricular hypertrophy

In conclusion we have presented a simple computer model which generates precordial QRS complexes very similar to those observed in normal man Furthermore simulated increases in left ventricular wall thickness and volume in the model caused changes in the calculated precordial QRS complexes which are characteristic of left ventricular hypertrophy The potential applications of the model are considerable

Summary

The cardiac electric field generated by depolarization of the human ventricle is simulated with a computer model which utilizes 1,500 dipoles The configuration of the ventricles utilized in the model assumed that the cross sectional shape of the left ventricle was circular and the right ventricular free wall was a portion of an ellipse The torso was assumed to be homogeneous and infinite The activation sequence was based on the measurements of Durrer The depolarizational wave was simulated by dipole layers The output of the model is presented as a standard multilead precordial ECG The ECG complexes generated by the model closely resemble the precordial QRS complexes of normal man Simulated increases in wall thickness (1 to 2 2 × control) were associated with changes in the calculated precordial QRS complexes which were characteristic of left ventricular hypertrophy Voltage (R in V_5 or V_6 and S in V_1) and QRS duration increased linearly as a function of calculated left ventricular mass Increases in ventricular activation time were related nonlinearly to changes in left ventricular mass and did not occur in the absence of a simulated increase in wall thickness The effects of simulated changes in left ventricular volume (0 6 to 3 0 × control) on the QRS complex were mainly dependent on the resultant increase in left ventricular mass This model may be useful in simulating the precordial QRS complexes that result from isolated or combined changes in ventricular volume or wall thickness or other disorders of the heart Furthermore, it may be useful whenever a simulation of a QRS generator is needed

We thank Drs Herman L Falsetti and Donald D Brown for reviewing the manuscript and offering many helpful suggestions We also thank Drs Georg Knorr and Francois M Abboud for their encouragement during the course of this investigation

APPENDIX

The formulas and expressions that are utilized in the model are given below The coordinate system was chosen in the following way The z

Effectiveness and hazard of endomyocardial biopsy in dogs Comparison of two methods

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Since Sakakibara and Konno[1] reported the technique of endomyocardial biopsy in 1962 several investigators have reported on this approach [2] and have considered it safe and without significant risk Nonetheless this procedure has not been accepted widely in part because the significance of biopsy results for diagnosis and patient management has not been clearly established Furthermore the feasibility and risks of the procedure have not been studied adequately in experimental animals

The present study served to evaluate two current methods of endomyocardial biopsy[1] [7] in the dog to assess the technical feasibility risks and adequacy of the specimens for histologic study

Materials and methods

Characteristics of biopsy forceps The Konno Sakakibara bioptome (Tonodura Ikakogyo Co Tokyo Cat No 9400) was used in seven male mongrel dogs, designated Group K, and a biopsy forceps designated B forceps originally designed for fiberoptic bronchoscopy and biopsy (Olympus Co N J FB C1) was used in seven dogs designated Group B The two instruments are compared in Table I

The Konno Sakakibara bioptome has been described in detail The method to introduce biopsy forceps through a sheath catheter has been described recently by several investigators. [7 8 9] The B forceps is similar to the bioptome but the shaft and tip are smaller in diameter which permits passage of the instrument through a No 9 French Brockenbrough or thin wall Cournand catheter In contrast to the bioptome this instrument does not have a proximal knurled knob and the sliding assembly and handle are made of plastic The cutting device at the distal tip made of stainless steel opens bidirectionally and is more oval and sharper than the bioptome

Biopsy procedures The femoral vein was isolated by cut down and the bioptome was advanced to the right ventricle under fluoroscopic guidance The right femoral vein was chosen in the first two dogs of Group K but the catheter frequently lodged at the right renal or hepatic vein because of its curvature and was difficult to advance further Insertions from the left femoral vein eliminated this problem The intracavitary electrocardiogram (ECG) was monitored to assess the catheter tip position [1 11] Once the catheter tip was positioned against the septum the tip was opened and then closed taking a bite of tissue Whenever the catheter was pulled back resistance or a tagging sensation was felt with sudden giving way as a tissue piece was torn off

In Group B for biopsy with the B forceps a No 9 Fr thin wall Cournand catheter was advanced to the right ventricle under fluoroscopy and monitoring of pressure This sheath catheter was inserted from the left femoral vein in two dogs The catheter was positioned in the right ventricle and then the B forceps was advanced through the catheter until its tip came out of the distal end of the sheath The tip was then opened

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6. Romhilt D W Bove K E Norris R J Conyers E Conradi [illegible] Rowlands D T and Scott R C A critical appraisal of the electrocardiographic criteria for the diagnosis of left ventricular hypertrophy Circulation 40 185 1969
7. Horan L G Flowers N C and Miller C B A rapid assay of dipolar extradipolar content in the human ECG J Electrocardiol 5 211 1972
8. Martin R D Cox J W Jr Keller F W Terry F H and Brody D Equivalent cardiac generator two moving dipoles and moving dipole and quadripole Ann Biomed Eng 2 164 1974
9. Okajima M Fujino T Kobayashi T and Yamada K Computer simulation of the propagation process in excitation of the ventricles Circ Res 23 203 1968
10. Horan L G and Flowers N C Simulation of the sequence of ventricular activation and the choice of an inverse solution Med Res Engin 6 28 1967
11. Ideker R E Brody D A Cox J W Jr and Keller F W Examination of multiple dipole inverse cardiac generator based on accurately determined model data J Electrocardiol 6 197 1973
12. d Alche P Ducimetiere P and Lacombe J Computer model of cardiac potential distribution in an infinite medium and on human torso during ventricular activation Circ Res 24 719 1974
13. Salu Y Computer simulation of the electrical activity of the heart J Theor Biol 43 43 1974
14. Thiry P S Rosenberg R M and Abbott J A A mechanism for the electrocardiogram response to left ventricular hypertrophy and acute ischemia Circ Res 36 92 1975
15. Selvester R H Collier C R and Pearson R B Analog computer model of the vectorcardiogram Circulation 31 45 1965
16. Plonsey R Bioelectric phenomena New York 1969 McGraw Hill Book Company Inc
17. Hoffman B F and Cranefield P F Electrophysiology of the heart New York 1960 McGraw Hill Book *Company Inc*
18. Sears F W Optics Reading Mass 1949 Addison Wesley Press
19. Selvester R H Kirk W L and Pearson R B Propagation velocities and voltage magnitudes in local segments Circ Res 27 619 1970
20. Durrer D van Dam R T Freud G E Janse M J Meyler FL and Arzbaecher R D Total excitation of the isolated human heart Circulation 41 899 1970
21. Eycleshymer and Schoemaker A cross section of anatomy New York 1930 D Appleton & Company
22. Gelerenter H L and Swihart J C Numerical computation of body surface potentials produced by an arbitrary distribution of generators in the heart *in* International Symposium on the Electrophysiology of the Heart October 1963 Milan
23. McPhie J Left ventricular hypertrophy Electrocardiographic diagnosis Aust Ann Med 7 317 1958
24. Allenstein B J and Mori H Evaluation of electrocardiographic diagnosis of ventricular hypertrophy based on autopsy comparison Circulation 21 401 1960
25. Liu C K and DeCristofaro D Sensitivity and specificity of electrocardiographic evaluation of LVH in 364 unselected autopsy cases AM HEART J 76 596 1968

Fig 1 Right ventricular endocardium of a dog from which six biopsy specimens had been taken Arrow indicates a small hemorrhagic spot on the septal wall where a specimen had been taken Chordae tendineae were cut when the heart was opened at autopsy

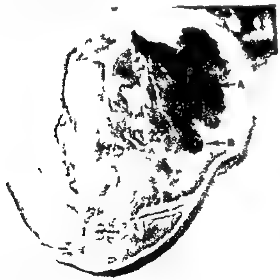

Fig 2 Right ventricular epicardial surface of a dog from which seven biopsy specimens had been taken Arrow *A* indicates hemorrhage on the epicardial surface of the outflow tract, and arrow B indicates a small perforation

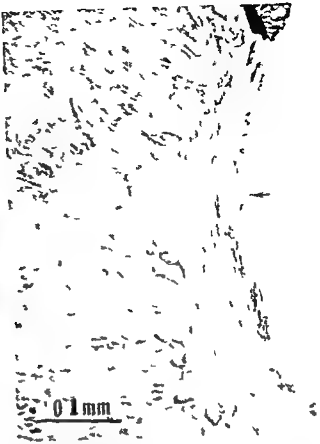

Fig 3 Endocardial aspect of biopsy taken by Konno bioptome stained with hematoxylin and eosin Arrow points to thickened endocardium

During 71 of 73 successful procedures ECG records were available The incidence of arrhythmias did not differ in the two groups (Table II) nor was it affected by the infusions No arrhythmia was seen in 16 per cent isolated VPBs occurred in 51 per cent and ventricular tachycardia was noted in 34 per cent of the biopsy attempts Two or more runs of ventricular tachycardia were seen in 14 per cent Temporary right bundle branch block appeared on one occasion in Group B and subsided after 5 minutes Recurrent short runs of ventricular tachycardia were observed for 3 minutes after the bioptome was withdrawn on one occasion in a Group K animal Transient falls of left ventricular or aortic pressure were recorded during arrhythmias

At autopsy some biopsy sites were identified as small holes on the endocardium and many were surrounded by a 0 5 to 2 cm hemorrhage into the endomyocardium (Fig 1) On one occasion perforation of the right ventricular outflow tract occurred resulting in hemopericardium but no tamponade (Fig 2)

Table I Characteristics of two biopsy forceps

	Konno Sakakibara bioptome (Cat No 9400)	*Bronchial biopsy forceps (FB 1C)*
Length (cm)	110	105
Shaft diameter (mm)	2 0	1 7
Tip diameter (mm)	2 5	1 72
Shaft	Covered with Teflon sleeve	Covered with coiled stainless steel wire
Distal tip	Curved	Straight

and specimens were taken Because of the spring character and straightness of the forceps the tip tended to enter the outflow tract Therefore, the approach through the right external jugular vein was chosen for the remainder of the animals in this group The tagging sensation was far less frequent in this approach compared to the bioptome, probably because the teeth are sharper and the tip is closed more tightly when it passes through the small outlet of the end hole catheter As soon as the biopsy had been obtained the B forceps was pulled out, and the sheath catheter stayed in the right ventricular cavity

Cleaning and sterilization of the bioptome are difficult especially when blood has been trapped in the Teflon sleeve [5, 10] Cleaning the B forceps was easier and more effective The whole shaft and tip were inserted into the sheath catheter and flushed with water at high pressure

Protocol Male mongrel dogs weighing 11 3 to 17 6 kilograms, were anesthetized with chloralose and urethane and maintained their own respiration on ambient air Lead II of the ECG was monitored throughout the procedure The left femoral artery was isolated by cut down, and a No 7 Fr Cordis pigtail catheter was advanced to the aorta and connected to a Statham P23D strain gauge transducer Systemic heparinization of the dog was carried out The ECG and left ventricular or central aortic pressure were recorded during and several minutes after the biopsy procedure with an Electronics for Medicine DR 8 recorder

The aim was to obtain at least four specimens in each animal, before, during, and after infusions of physiologic saline solution, with or without added ethanol Five to nine attempts yielded three to seven specimens in each dog The time required for each biopsy was measured from the insertion of the biopsy catheter to its withdrawal One specimen from each animal was blotted on dry gauze and weighed with a Mettler balance Model H54

One to three specimens were preserved in 10 per cent buffered formalin immediately after the removal of the catheter Twenty eight specimens in all were examined after staining with hematoxylin and eosin Six specimens were prepared for electron microscopy The specimens were fixed immediately with 3 per cent glutaraldehyde in 0 2M cacodylate buffer, washed with 10 per cent cold sucrose in 0 2M cacodylate buffer, and postfixed with 1 per cent osmium tetroxide The dehydration was carried out with 50 75, 95, and 100 per cent ethanol and then propylene oxide The tissue was imbedded in fresh Epone Final sections for electron microscopy were chosen according to the results of light microscopic examinations that showed the area contained artifact free, longitudinally oriented muscle cells Ultrathin sections were obtained with a Sorrall Porter Blum ultramicrotome stained with uranyl acetate and lead citrate, and examined with a Phillips 200 electron microscope

The rhythm records obtained during the biopsy were classified as follows (1) no arrhythmias (2) isolated ventricular premature beats (VPB s), (3) ventricular tachycardia, defined as more than three VPB's in a row

Approximately 4 hours elapsed from onset of anesthesia to the last biopsy Ten animals were put to death immediately three animals after 3 days, and one animal 1 week later, by intravenous injection of 50 per cent magnesium sulfate solution Careful observations of the presence of pericardial hemorrhage, external bruising, and internal trauma to the right atrium ventricle, and septum were made

Results

In Group K animals biopsy was attempted with the Konno bioptome 44 times with 36 successes (82 per cent) In Group B, 45 attempts with the B forceps yielded 37 successes (82 per cent) The time required for successful biopsies was 170 ± 12 seconds (mean ± SEM) in Group K and 115 ± 14 seconds in Group B ($p < 0 001$) The weights of the specimens ranged from 1 9 to 4 5 mg (mean ± SEM 2 6 ± 0 4 mg) in Group K and from 0 3 to 1 8 mg (1 1 ± 0 3 mg) in Group B ($p < 0 005$)

human cases Recently Ali[5] reported the use of a gastrointestinal biopsy catheter with No 12 or 13 Fr end hole sheath catheters with 100 per cent success. This technique was employed by Alexander and Gobel to obtain biopsy specimens in patients with idiopathic hypertrophic subaortic stenosis. A similar approach was reported by Richardson[7] using bronchial biopsy forceps with sheath catheter and employing this method Olsen reported that the clinical diagnosis was confirmed in 32 per cent excluded in 33 per cent and unhelpful in 28 per cent of 67 cases there were 7 per cent failures The St Joseph Hospital group in London has used the same technique[9] Caves and associates[6, 5, 26] modified the Konno bioptome for the detection of early rejection of transplanted hearts in dogs[5] and man and more recently Rider and associates[27] have widened the indications for this procedure

The present experimental study was undertaken to compare the efficacy and safety of two techniques presently in use The bronchial biopsy forceps stood out for its convenience and ease of application resulting in a significantly shorter time for the procedure The Konno bioptome on the other hand yielded significantly larger specimens The two techniques did not differ in effectiveness arrhythmogenicity myocardial lesions, or distortion of specimens

In the 1940s when Cournand and his associates[4] developed cardiac catheterization many investigators found endocardial hemorrhage in dogs and hesitated to apply the procedure clinically This phenomenon turned out to be transient if not species specific Several autopsy examinations after endomyocardial biopsy have been reported According to Somers and associates[3] six patients died unrelated to the procedure 2 days to 4 years after biopsy and no recognizable sites of damage could be identified

The high incidence of ventricular arrhythmias may impose some limitations upon the clinical use of this technique and render careful electrocardiographic monitoring obligatory However isolated VPB s and runs of VPB s occur frequently during right heart catheterization and are not considered a contraindication to proceed

Distortion and fragmentation of tissue have not been quantitated in other reports Ali and associates stated that they did not see any such changes We believe that this is a limitation inherent in the technique and that for adequate tissue diagnosis at least two or more samples of myocardium from different sites should be obtained

Summary

Two different methods of endomyocardial biopsy were evaluated Compared to the Konno bioptome a technique using a biopsy forceps originally designed for fiberoptic bronchoscopy and bronchial biopsy passed through a No 9 Fr end hole catheter was easier to perform The biopsy device is smaller than the Konno bioptome has sharper teeth and is easier to clean The two techniques did not differ in arrhythmogenicity hemorrhagic changes in the myocardium or distortion of the specimens Ventricular tachycardia as defined by three beats in a row was observed in 34 per cent Epicardial hemorrhage was seen in nine of 14 animals and the specimen distortion rate was 43 per cent In one animal perforation of the right ventricle and hemopericardium occurred

The authors wish to thank Kathryn A Thorp for technical assistance and Klara Rev for processing the tissues for electron microscopy

REFERENCES

1 Sakakibara S and Konno S. Endomyocardial biopsy Jap Heart J 3 537 1962.
2. Takatsu, T., Kawai, C., Tsutsumi, J and Inoue, K A case of idiopathic myocardiopathy with deposits of a peculiar substance in the myocardium diagnosis by endomyocardial biopsy AM HEART J 76 93 1968
3 Somers, K Hutt M S R., Patel A K and D Arbeea P G Endomyocardial biopsy in diagnosis of cardiomyopathies, Br Heart J 33 822, 1971
4. Ali, N., Ferrans, V J Roberts, W C and Massumi, R. A Clinical evaluation of transvenous catheter technique for endomyocardial biopsy Chest 63 399 1973
5 Ali, N Transvenous endomyocardial biopsy using gastrointestinal biopsy (Olympus GFB) catheter AM HEART J 87 294 1974
6 Caves, P K. Schulz, W P Dong E Jr., Stinson E B., and Shumway N E. New instrument for transvenous cardiac biopsy Am J Cardiol. 33 264 1974
7 Richardson, P J King s endomyocardial bioptome Lancet 1 660 1974
8 Alexander C S and Gobel, F L Diagnosis of idiopathic hypertrophic subaortic stenosis by right ventricular septal biopsy Am. J Cardiol. 34 142, 1974
9 Brooksby I A. B Swanton R. H Jenkins, B S., and Webb-Peploe M. M Long sheath technique for introduction of catheter tip manometer or endomyocardial bioptome into left or right heart Br Heart J 36 908 1974
10 Brooksby I A. B Jenkins, B S., Coltart D J., and Webb-Peploe M M Left ventricular endomyocardial biopsy Lancet 2 1222 1974
11 Konno S., and Sakakibara, S Endo-myocardial biopsy Dis. Chest 44 345 1963
12. Sekiguchi, M and Konno S Histological differentia

Table II Complications of biopsy and quality of specimen for light microscopy

Group	Arrhythmias associated with biopsy†							Autopsy findings			Quality of specimen			
	No of procedures	NA		VPB		VT		No of animals	Epicardial lesion		No of specimens	Quality		
												Good	Distorted	
		No	%	No	%	No	%		No	%			No	%
K	35	[illegible]	17	17	48	12	34	7	5	71	9	5	4	44
B	36	[illegible]	14	19	53	12	33	7	4	57	19	11	8	42
Total	71	11	16	36	51	24	34	14	9	64	28	16	12	43

Group K = Biopsy was done with Konno s Bioptome Group B = Biopsy was done by bronchial biopsy forceps with sheath catheter
†NA = no arrhythmias, VPB = ventricular premature beats, VT = ventricular tachycardia

Histological studies were carried out in 28 specimens with light microscopy and in six specimens with electron microscopy There was no difference in the quality of the specimens between the two groups Five specimens for light microscopy were unsuitable for diagnosis because of fragmentation Seven samples (25 per cent) showed slight distortion and hemorrhagic changes Sixteen of 28 (57 per cent) samples were considered perfect for histological studies of endocardium and myocardium One animal was found to have thickening of endocardium and subendocardial fibrosis (Fig 3) Thus, the incidence of artifactual distortion of the sample was 43 per cent

All electron microscopic samples were of good quality and all showed myocardium in the systolic phase

Discussion

The clinical application of cardiac biopsy has not been fully established Its diagnostic usefulness is limited to certain specific diseases involving mainly endocardium and myocardium Unless the myocardial pathology is diffuse a biopsy specimen may fail to reveal its presence Even if a specific pathological diagnosis is established, cardiomyopathies only rarely respond to specific therapy, except perhaps in cases of acute subacute, or chronic myocarditis, Loffler s endomyocarditis, cardiac sarcoidosis hemochromatosis, or hypertrophic cardiomyopathy [11 13] However, a technique which permits safe serial study of myocardium with light and electron microscopy, histochemistry, and immunological methods is considered most desirable for further elucidation of the pathogenesis and course of the cardiomyopathies [14 15]

Several different techniques have been used for myocardial biopsy Price and associates[16] reported a percutaneous transthoracic technique in experimental animals using a Vim Silverman biopsy needle One of 19 animals died during the procedure, and three which were killed immediately after the procedure showed evidence of hemopericardium Weinberg and associates[1] described five cases of myocardial biopsy under thoracotomy and local anesthesia Bercu and associates[1] used a transthoracic method to obtain left ventricular septum by means of a modified Menghini needle in 10 dogs and in 10 patients Two of the dogs died 3 and 14 days after the procedure and in one tricuspid perforation was found Several other investigators reported similar techniques under local or general anesthesia using open thoracotomy or transthoracic needle biopsy [19] Although there was no serious complication in 54 consecutive transthoracic needle biopsies reported by Sutton and Sutton [1] there are inevitable risks of pericardial hemorrhage pneumothorax as well as anesthesia

Since Sakakibara and Konno[1 11] reported transvenous endomyocardial biopsy with the Endomyocardial Bioptome several investigators have considered this to be the most feasible and safe procedure [4] Sakakibara and Sekiguchi[11] have performed more than 500 procedures without death or significant complications Somers and associates[3] reported their experience of 64 patients without significant risk, and Ali and associates[4] reported 28 patients with 26 successes and no complications

Bulloch and associates [1] using a cutting needle through a sheath catheter reported one tricuspid perforation in 18 dogs and one complication of permanent right bundle branch block in 20

A test experience with a machine processed electrocardiography diagnosis: The recognition of "normal" and some specific patterns

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There are a number of commercially available computer based diagnostic services for electrocardiographic (ECG) interpretation and the clientele have included forward looking staffs of community hospitals. One of the services subscribed to by some hospitals in the Minnesota area was made available to us in the spring of 1975 by the company which provides similar services to a sister hospital. This assessment of its value follows. The established practice at Northwestern Hospital in Minneapolis for ECG interpretations has been a rotation of readers from a large panel of physicians approved by a committee of the hospital. The trial period was introduced without preliminary discussion of the specific objectives of the trial or any coaching regarding the language of the system. This method of implementating the method may account for the fact that some of the reader group expressed early hostility to the operation. Whether an introductory session for discussion of the method and the distributing of the IBM general information manual would have altered greatly the reactions of the readers is conjectural.

For assessment of the system's reliability, its capability of a detection of abnormality, and its accuracy in correctly identifying an abnormality, 500 consecutive records to which were attached on separate pages the computer readout and the interpretation of the routine physician reader were collected. The primary objective of the study was to determine whether the computer readout should be reviewed before its issuance to the practicing physician and its incorporation in the permanent record of the patient. The study was not a statistical analysis of inter observer differences although the report is based mainly upon the differences in the ECG interpretation of one of us (H. B., the reviewer) with those of the computer. On preliminary survey it was apparent that differences would be difficult to code, to quantitate, and to index because of lack of a common language and agreed upon definitions of diagnostic phrases. There were instances early in the operation which invited the conclusion that the computer readout of this system would require over reading by the physician. However, the interpretations generated by computer seemed to be a valuable adjunct to the physicians' interpretations in some instances and probably a stimulus for the study of scientific advances in electrocardiology generally.

The profession is well aware of the difficulties which have existed for over a decade regarding computer reading of ECG's, for example, the analysis by Bailey and associates[2] and the acridly expressed denunciation of the method by some clinicians with exceptional electrocardiographic expertise—for example, Marriott.[3] The poor correlation in the studies of the computer diagnosis and the physician's diagnosis has received wide attention. The present status of computer science applied to electrocardiology has been recently reviewed by Pipberger and associates[4] and the reasons for the continued difficulties and physicians' misunderstandings of the methods were pointed out. These authors began and ended their

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[1] Cardiopulmonary Incorporated, Minneapolis, Minnesota, using an IBM Bonner ECG program.

tion employing endomyocardial biopsy in the clinical assessment of primary myocardial disease Jap Heart J 10 30 1969
13 Sakakibara S and Sekiguchi M Wider application of the endomyocardial biopsy technique Ann Thorac Surg 16 429 1973
14 Kawai C Idiopathic cardiomyopathy A study on the infectious immune theory as a cause of the disease Jap Circ J 35 765 1971
15 Goodwin J F Prospects and predictions for the cardiomyopathies Circulation 50 210 1974
16 Price K C Weiss J M Hata D and Smith J R Experimental needle biopsy of the myocardium of dogs with particular reference to histologic study by electron microscopy J Exp Med 101 687 1955
17 Weinberg M Fell E H and Lynfield J Diagnostic biopsy of the pericardium and myocardium Arch Surg 76 825 1958
18 Bercu B Heinz J Choudhry A S and Cabrera P Myocardial biopsy—a new technic utilizing the ventricular septum Am J Cardiol 14 675 1964
19 Raffensperger J Driscoll J F Sutton G C and Weinberg M U Jr Myocardial biopsy Arch Surg 89 1021 1964
20 Timmis G C Gordon S Baron R H and Brough A J Percutaneous myocardial biopsy Am Heart J 70 499 1965
21 Sutton D C and Sutton G C Needle biopsy of the human ventricular myocardium Review of 54 consecutive cases Am Heart J 60 364 1960
22 Bulloch R T Murphy M L and Pearce M D Intracardiac needle biopsy of the ventricular septum Am J Cardiol 16 227 1965
23 Bulloch R T Pearce M B Murphy M L Jenkins B J and Davis J L Myocardial lesions in idiopathic and alcoholic cardiomyopathy Study by ventricular septal biopsy Am J Cardiol 29 15 1972
24 Olsen E G J Diagnostic value of the endomyocardial bioptome Lancet 1 658 1974
25 Caves P K Billingham M E Schulz W P Dong E Jr and Shumway N E Transvenous biopsy from canine orthotopic heart allografts Am Heart J 85 525 1973
26 Caves P K Stinson E B Billingham M and Shumway N E Percutaneous transvenous endomyocardial biopsy in human heart recipients Ann Thorac Surg 16 325 1973
27 Rider A K Billingham M E and Harrison D C Small vessel coronary disease Biopsy evidence of intramyocardial arteriopathy Circulation 50 (Suppl 3) 109 1974
28 Cournand A Bing R J Dexter L Dotter C Katz L N Warren J V and Wood E Report of committee on cardiac catheterization and angiography of American Heart Association Circulation 7 769 1953

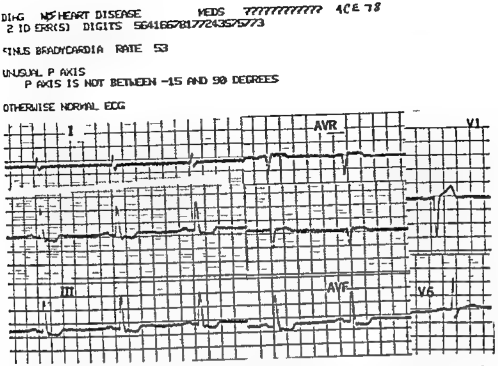
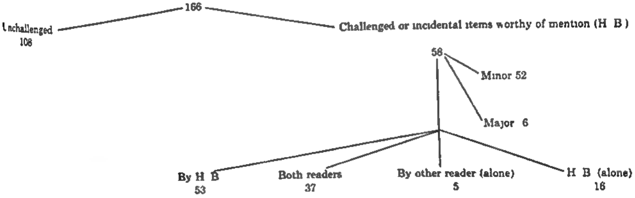


Fig 2 ECG reported "normal" by the computer but may be seen to have a gross ST T change and a slight intraventricular conduction defect (A repeat ECG the following day showed the same basic pattern with a 0 5 mm increment in the ST shift and the computer reported the abnormality) The patient was a 78-year-old man with the history of hypertension mild diabetes and effort chest pain who was on digitalis medication

Table II Normal ECG (by computer)



ered to be important errors (false negatives)—3 6 per cent In each of these six cases the routine physician reader had independently identified the tracing as abnormal The abnormalities observed are charted in Table I and two of the tracings are illustrated (Figs 1 and 2)

In an additional 52 tracings (see Table II) one of us (H B —hereafter called the reviewer) believed that there were items of minor nature worthy of mention though in a large percentage of them unlikely to have major clinical significance

These variants did not include slight axis shifts minor P wave abnormalities small U waves or occasional atrial or ventricular premature beats The main categories of aberrances or variants thought worthy of mention by the reviewer were minor intraventricular conduction defects (13)

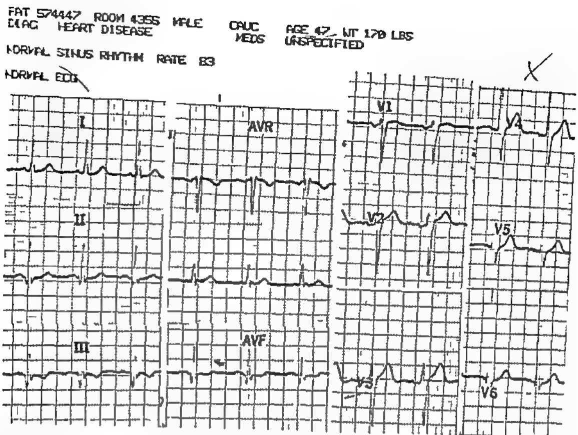


Fig 1 ECG reported normal by computer processing but believed to indicate an old inferior infarction by H B and independently by routine reader (lower script) The voltage and duration of Q aV_F and the duration of RV,V are the *main markers* the slight intraventricular conduction aberation is consistent The voltage criteria (RV + SV > 40 mm) for LV *hypertrophy are present* H B s interpretations were made blind to clinical diagnosis The patient was a 44 year old man with the history of effort chest pain and hypertension in whom the right coronary artery of native dominance showed total occlusion in its proximal third and the left main artery was 50 per cent narrowed in diameter with milder lesions distally There was akinesia of the basilar half of the diaphragmatic wall

Table I Six major items—computer missed

	No
Inferior infarct	2
Gross ST shift	1
Gross T abnormality	1
High probability RVH	1
Sinus Wenckebach	1

review with comment regarding an editorial by Craige[5] who pointed out the reliability of well trained technician readers For many years at the Mayo Clinic, one of us participated in what seemed to be a successful program wherein the senior ECG technicians gave a descriptive reading of the tracing mentioning any departures from normality, without a clinical diagnosis The clinical implications were made by the patient s physician and, in a groping amateur way he arrived at probabilistic diagnoses This method incidentally, was not favored by hospital accreditation reviewers

The exploration of methods to correlate meaningfully, at the Minneapolis Northwestern Hospital the diagnosis of the computer with that of a routine physician reader, and to one of us (H B), led to frustrations until the following simplified questions were posed These questions directly addressed the primary objective of our review—the need for a routine check on the computer interpretation by a physician

1 *If* the reports of a computer readout were simply normal ECG
   a Was the diagnosis reliable?
   b Was there additional information in the tracing which would be deserving of mention?
2 If samplings of certain computer generated diagnostic categories were reviewed (e g anterior and inferior infarctions, atrial fibrillation) what was the level of agreement with our (H B s) interpretation?

In the group of 500 tracings the computer readout was unequivocably normal ECG in 166 instances (32 per cent)

In six of these 166 tracings there were consid

rhythm in these was a sinus mechanism in five and a fixed rate pacemaker with interplay of sinus and electronic paced beats in the other In one instance Wenckebach periods were present in another the PR interval was short with QRS being normal In the other three instances no reason for the lack of recognition of the sinus rhythm was evident

The language of the IBM Bonner program (as it was expressed in the reporting of myocardial infarction) localized the lesion as anterior ante roseptal anterolateral inferior and true poste rior Preceding the word infarction there was always one of the following modifying terms viz possible consistent with consid er cannot be excluded It is noteworthy that the terminology did not include a positive or definitive diagnosis or a numerical clue which would give the physician a probability (or confi dence index) of a suggested diagnosis of infarc tion. The assessments of these cases by H B were as shown in Table V

When the reviewer s combined groups assessed as indicative and highly probable are compared with the computer s possible and consistent with the reviewer s assessment agreed with the computer program in only 22 of 37 cases (60 per cent) of anterior infarction suspects but in 30 of 34 cases (90 per cent) of inferior infarction suspects

It is noteworthy—and without good explana tion—that the computer s designation of possi ble was a stronger term in the reviewer s opinion (more sensitive and more specific) in suspected inferior infarctions than in anterior infarctions *A priori* we would have suspected more overcall by the computer of inferior infarctions (because of Q waves *III*) than in anterior infarctions but the data showed an opposite situation i e more false calls for anterior than posterior lesions This problem seemed largely related to the nonrecog nition of small R waves in V V particularly in cases where left ventricular hypertrophy with a strain effect was suspected One case of electronic pacing was called consistent with anterior infarct another example of an error with which the laboratory scientist is more comfortable than the clinician

Fairly numerous computer interpretations in cluded suggestions of both anterior and inferior infarctions but without the computer giving a probability value to the suggestions it is difficult to render critical assessment of the interpreta tion Certainly there was enough in the records to justify thoughts of double lesions In the group of 500 tracings it was rare for the computer to read L V hypertrophy the printout of LVH with strain (possible or consistent with) occurred nine times and was concurred in by the reviewer as a typical pattern of such in eight of them Four tracings (2 4 per cent) in the carefully analyzed group called normal by the computer showed errors in the transcription between the data the ECG technician keyed into the terminal and which the computer accepted and the data impressed on the ECG as to patient identifica tion We did not accumulate the percentage of bad or incomplete telephone transmission which was considerable Many such difficulties we feel sure represent early inexperience as might be expected on a learning curve

Comment

This study points out the general unsatisfac tory state of clinical ECG correlations Our own bias has been a long time support of machine processing—not because of expectations of error free performance but because it should lead to standardization of terminology and repeatibility of the ECG label and eventually allow an aberra tion to acquire a worthwhile probability rating as to its significance In addition we are convinced that the teaching of scientific electrocardiog raphy is aided by the discussion of machine processing problems With computer processing vectorcardiograms may also be beautifully repro duced from the stored tapes when triaxial lead systems are used A further dividend of value is the facilitation of stenographic work One major drawback to computer reading as generally used contrasted with the human interpretation is the absence of comparisons with previous records The importance of this is not to be denied but may have been overemphasized we believe in respect to the percentage of cases where it would be important If this requirement became manda tory as might eventually be decided affirmative ly the computer program necessarily would become more complex although still within the capability of existing technology

One of us (H B) closely observed the develop ment of the Mayo Smith system and his diag noses correlated well there He has also been privy to the independent program of computer

Table III Sixteen minor items mentioned by H B, not by routine reader

	No
IVCD	5
ST segment shift	4
T >> T	3
High RV	2
Absent RV + LAE	1
Absent RV	1

Table IV Computer comments and reviewer assessments

Computer comment	*No*	*Quite significant (H B)*
Low voltage T waves	7	0
Low voltage QRS	3	0
Left axis deviation (30 45)	3	3
Right axis deviation (91 180)	1	0
Possible inferior infarction	2	2
Consider anteroseptal infarction	1	0
Intra atrial block	1	1
Intraventricular conduction defect (130 ms)	1	1
ST segment abnormality	1	0
	20	7

slight ST shifts (11) and possible posterior inferior infarction suspects (seven) If this reported incidence of minor abberrations appears high it could be possibly related to the group being a hospital population with many elderly persons, the average age was 57 years with S D of ± 15 years (77 males, average age 57 ± 15 years 85 females 57 ± 16 years) The conclusion is suggested that the computer was not programmed to report minor aberrations (i e insensitive) and that probably there was a built in avoidance of over reading the tracings The existence or otherwise of agreement of the routine reader with the reviewer was later correlated this correlation is shown in Table III It is evident that the reviewer thought more minor variations would be worth mentioning but in the tracings considered borderline the differences with the routine reader were infrequent

In a secondary survey of the diagnostic sheets 20 instances were noted where there was a computer commentary, but the routine physician reader appeared to emphasize normal

Table V Computer designations and reviewer assessments

Computer designation	*No*	*H B assessment*			
		Indicative	*High probable*	*Low probable*	*Negative*
General group of anterior infarctions					
Possible	12	1	2	7	2
Consistent with	25	17	2	4	2
Consider	11	0	0	4	7
Cannot be excluded	1	0	0	0	1
Total	49	18	4	15	12
General group of inferior infarctions					
Possible	13	[illegible]	2	2	0
Consistent with	21	15	4	2	0
Consider	[illegible]	2	2	5	0
Total	43	26	8	9	0

ECG —perhaps implying the computer comment unworthy of mention The computer comments are listed in Table IV together with an assessment of whether the mention of them was considered worthy by the reviewer In a third of the cases the reviewer believed that the item deserved mention

In the 500 tracings the diagnosis of atrial fibrillation was made in 32 This was agreed to by the reviewer in 26 instances It is probably generally appreciated that computer based analysis of arrhythmias is much more difficult than the analysis of wave forms of PQRST With a physician s analysis of any irregularity being mandatory, there is a doubt that the necessary programming to improve computer accuracy in arrhythmia definition will pay worthwhile dividends in clinical practice The computer call of atrial fibrillation when such was *not* present is a serious fault only if the practitioner receiving and accepting the diagnosis initiates therapy with grievous consequences e g digitalis being incorrectly used The correct diagnoses in the six instances of error in computer interpretation were as follows shifting atrial pacemaker (same patient twice) 2 ventricular premature beats with escape junctional beats 2 junctional and sinus rhythm interplay 1 sinus rhythm—prolonged PR (0 30) 1

There were six instances where the computer printout was ' undetermined rhythm and the

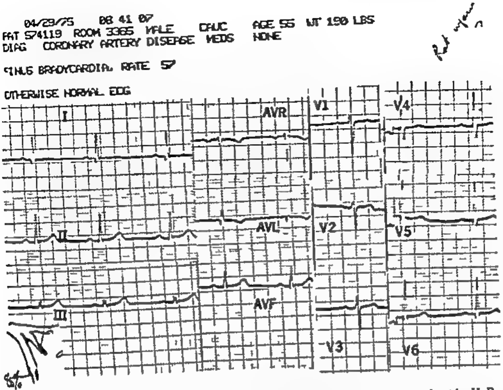


Fig 4 ECG reported normal by the computer and routine reader but judged borderline at least by H. B from the rightward shift of T axis in the frontal plane (T > T) and a Q wave and negative T in aV_L. A later review of clinical record revealed the main complaint to be effort pain and coronary arteriography showed obstructive coronary disease as illustrated in the diagram lower left a complete proximal obstruction of large angular branch and approximately 80 per cent luminal obstruction in anterior descending

lems the Bonner IBM ECG diagnostic program is conservative in concordance with the admonition of Pipberger and associates i e the hope that computers will not contribute to this disease heart disease of ECG origin the seriousness of which cannot be overemphasized

It is recognized that a blinded study by readers with observer/computer interpretations being compared by an independent observer is a superior method of studying interobserver differences The analyst however will have difficulty in determining when there were mere differences in language (i e terminology) and in equivalence of probability without numbers being assigned but have less difficulty in judging the true vital differences in interpretation The simple approach utilized in this study assumes that the cardiologist (H B) is superior to the specific system being scrutinized that is the IBM Bonner program which was in effect in April 1975 It would only be fair for H B to be challenged regarding his interpretations with request for criteria particularly as the criteria are made available by the alternative computer method However this is not the specific problem being addressed One point regarding diagnostic criteria deserves emphasis namely in addition to the importance of Q waves of 30 ms or more in duration the ST contour with or without a shift in the level with deeply inverted T wave often adds to strength of the diagnosis of infarction The ST T configuration was one emphasized half a century ago by Pardee[11] and the voltage of T wave and T axis was believed important by Burch[3] and by Ashman and Hidden despite the known vagaries of T wave changes Eventually minor aberrations in QRS ST and T may be assigned clinical significances These may loom larger in importance to epidemiologists than clinicians for example age related left axis deviation and premature ventricular beats which may be interrelated[5]

The tracings were read by H B without any clinical data If either a reader or computer is given information on age sex weight history of heart disease blood pressure clinical diagnosis

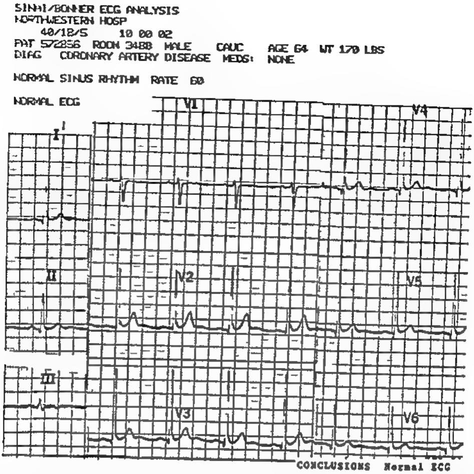


Fig 3 ECG with computer print out of "normal" agreed with by the routine reader Independent assessment by H B was "borderline" because of the unusually prominent anterior vector in horizontal plane (RV V) This tracing was at first suspected to be a result of a technical phenomenon from excessive use of electrode paste on the chest forming a large common electrode however repeat tracings were similar Curiously after a bypass graft to a severely obstructed left anterior descending artery the QRS display in chest leads showed a more usual pattern This pattern could be explained by abnormal excitation of the septum if there were a blocked middle fascicle of the left bundle and a strong apex to base septal vector

processing and diagnostic readout developed at the University of Minnesota Hospital under Tuna [6] and has had some contact with collaborative veterans hospital program, utilizing the Pipberger system, through discussions with Richman at the Minneapolis Veterans Hospital The good correlation of the human reader to the computer performance when the physician has had some input into the programming may be expected, as Pipberger and associates[4] pointed out, with a poorer correlation being found when the physician reader has had no relations with the development of the system As Wilson and associates[5] pointed out 30 years ago ECG science is exact, but its clinical utilization is often wretched Reviewers from outside the electrocardiology discipline, e g Koran,[9] appear more startled than those inside it with the reported interobserver variation in ECG interpretations The latter should know how inadequately correlated are the clinician s ECG diagnostic catechisms The problems stem from the following (1) There is often much more information in the minutiae of the ECG than is of direct clinical usefulness in diagnosis prognosis and treatment (2) The limits of normal have been difficult to define and the concept of late age changes being "normal for age" has we believe been conceptually wrong (though useful clinically)[1] (3) There have been variations in terminology and lack of clear definitions of terms (4) Correlative studies have pertained to "proof" wherein correctness of the ECG diagnosis has been assumed from clinical diagnosis (5) There has been reluctance to mention minor variants or abnormalities occurring with age when prognosis is not greatly if any changed for fear of creating anxiety—putting the patient unfairly at risk regarding occupation or jeopardizing his life insurance plans

In connection with the last mentioned prob

Case reports

Dissection of the aorta complicating intra-aortic balloon counterpulsation

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Intra aortic balloon counterpulsation has been used in support of patients with severe left ventricular dysfunction following myocardial infarction or cardiac surgery [1] The ease of application resultant hemodynamic benefit and relative safety have permitted increasing application of the device Complications have included vascular insufficiency of the catheterized limb aortic wall damage thrombocytopenia embolic phenomena and balloon rupture with gas embolus.[2] This report describes the occurrence of a dissecting aneurysm of the aorta adjacent to the location of a balloon catheter used for temporary hemodynamic support

Case report

A. A was a 61 year old white man in excellent health without past history of hypertension or known cardiovascular disease until Nov 22 1974 when he was admitted to an outlying hospital with an acute anteroseptal myocardial infarction. The initial course was complicated by frequent multifocal ventricular premature contractions and two episodes of ventricular tachycardia treated with intravenous lidocaine therapy The presence of pericarditis was described on the seventh and eighth hospital days. The patient was discharged after [illegible] days of hospitalization on procainamide 250 mg. every 3 hours and coumadin therapy On Dec 19 1974, the patient was readmitted to the same hospital because of recurrent syncopal episodes Cardiomegaly and pulmonary râles were noted. Treatment with digoxin and furosemide was instituted. On the second hospital day the patient developed ventricular fibrillation which was successfully reverted with precordial shock and lidocaine therapy was again instituted. On the following day recurrent ventricular tachycardia occurred and procainamide therapy was increased to 500 mg. every 3 hours. On the seventh hospital day multiple episodes of ventricular tachycardia were again observed The patient became hypotensive and was transferred to Strong Memorial Hospital

Upon admission the patient was found to be pale with cold, clammy extremities, but awake Systolic blood pressure was 60 mm. Hg by palpation. There was a sinus tachycardia of 110 per minute and the respiratory rate was 24 The jugular venous pressure was normal. There were pulmonary râles at both bases. Cardiac examination revealed a diffuse apical impulse in the sixth intercostal space at the anterior axillary line There was a visible as well as palpable dyskinetic impulse in the third and fourth left intercostal spaces. A Grade 2/4 pansystolic murmur was heard at the apex with radiation to the axilla A loud ventricular gallop was audible. There was no hepatosplenomegaly or peripheral edema

The electrocardiogram (ECG) showed sinus rhythm right bundle branch block, left axis deviation and Q waves in V and V consistent with a recent anteroseptal infarction. Chest x ray demonstrated cardiomegaly with the appearance of a left ventricular aneurysm. The patient underwent right heart catheterization with a flow-directed No 7 Swan-Ganz catheter via right antecubital vein cutdown An 18 gauge Longdwell cannula was inserted into the left brachial artery Intravascular pressures were recorded using Statham SP37 strain gauge transducers with a direct writing Clevite Brush recorder Brachial artery pressure was 78/52, PA pressure was 40/26 pulmonary wedge pressure 26 and right atrial pressure 5 mm. Hg The cardiac index measured by thermal dilution was 1.9 L./min /M

Under local anesthesia, intra aortic balloon counterpulsation was instituted via a right common femoral aortotomy with a 10 mm woven Dacron sidearm graft and an AVCO 40 ml. balloon advanced under fluoroscopic control to a position below the transverse aortic arch (Fig. 1) The patient's blood pressure and rhythm were stabilized on intra aortic balloon support and antiarrhythmic therapy prior to coronary angiography and left ventriculography Angiographic study showed a large aneurysm of the anterior and apical portion of the left ventricle with significant mitral regurgitation. Multiple episodes of ventricular tachycardia were observed despite antiarrhythmic therapy and intra aortic balloon counterpulsation

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and medications, the interpretation will be more often judged "right," which is pragmatically good, but it muddles the electrophysiologic science per se. Two ECG's reported normal by the computer and the routine reader demonstrate patterns which are of particular interest to us and should have had, in our opinion, the designation of at least "borderline." One shows a marked aberration of the QRS with a prominent anterior vector (Fig. 3) and the other a prominent right axis T shift (T_3 markedly higher than T_1, Fig. 4). It deserves mention that occasionally the computer did score a "triumph" over the routine physician reader, e.g., in suggesting a pericarditis complicating an infarction.

Summary

Five hundred ECG's machine processed by the commercially available IBM Bonner-Mt. Sinai System have been reviewed. The diagnostic printouts were of value as an adjunct to the physician's interpretations, but were not sufficiently reliable—in regard to either sensitivity (identification of the abnormal or borderline) or specificity (accuracy in predicting typical abnormalities)—to allow us to condone any claim for it being an independent reliable diagnostic service to noncardiologist clinicians.

Despite this disclaimer for current diagnostic reliability of ECG computer analyses, specifically the IBM Bonner system, we continue to be of the firm conviction that progress through this method of ECG analysis will have much to contribute in future years.

REFERENCES

1. Health care support/electrocardiogram (ECG) analysis program physician's guide, ed. 1, IBM, 1974.
2. Bailey, J. J., Itscoitz, S. B., et al.: A method of evaluating computer programs for electrocardiolographic interpretation. Application to the experimental IBM program of 1971, Circulation 50:73, 1974.
3. Marriott, H. J. L.: Digression on computers. Workshop in electrocardiography, Oldsmar, Fla., 1972, Tampa Tracings, p. 382.
4. Pipberger, H. B., Dunn, R. A., and Berson, A. S.: Computer methods in electrocardiography, Ann. Rev. Biophys. Bioeng. 4:15, 1975.
5. Craige, E.: On reading electrocardiograms, Circulation 49:1026, 1974.
6. Tuna, N.: Unpublished data.
7. Richman, H. G., and Brohert, C. R.: Evaluation of a statistical decision program for automated ECG processing (Pipberger program), Proc. Clin. Vectorcardiol., 1975.
8. Wilson, F. N., Rosebaum, F. F., and Johnston, F. D.: Interpretation of the ventricular complex of the electrocardiogram, Adv. Int. Med. 2:1, 1947.
9. Koran, L. M.: The reliability of clinical methods, data and judgements, II, N. Engl. J. Med. 293:695, 1975.
10. Simonson, E.: Differentiation Between Normal and Abnormal in Electrocardiography, St. Louis, 1961, The C. V. Mosby Company.
11. Pipberger, H. B., McCaughan, D., et al.: Clinical application of a second generation computer program, Am. J. Cardiol. 35:597, 1975.
12. Pardee, H. E. B.: Clinical aspects of the electrocardiogram, ed. 4, New York, 1974, Paul B. Hoeber, Inc., p. 156.
13. Burch, G. E.: Primer on electrocardiography, Philadelphia, 1955, Lea & Febiger, Publishers, p. 109.
14. Ashman, R., and Hidden, E.: Rightward axis of the T wave as an index of myocardial disease, Ann. Intern. Med. 12:1682, 1939.
15. Watanabe, Y., Pamintuan, J. C., and Dreifus, L. S.: Role of intraventricular conduction disturbances in ventricular premature systoles, Am. J. Cardiol. 32:188, 1973.

Case reports

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Intra aortic balloon counterpulsation has been used in support of patients with severe left ventricular dysfunction following myocardial infarction or cardiac surgery [1-4] The ease of application resultant hemodynamic benefit and relative safety have permitted increasing application of the device Complications have included vascular insufficiency of the catheterized limb aortic wall damage thrombocytopenia embolic phenomena and balloon rupture with gas embolus.[3] This report describes the occurrence of a dissecting aneurysm of the aorta adjacent to the location of a balloon catheter used for temporary hemodynamic support

Case report

A. A. was a 61 year-old white man in excellent health without past history of hypertension or known cardiovascular disease until Nov 22 1974 when he was admitted to an outlying hospital with an acute anteroseptal myocardial infarction. The initial course was complicated by frequent multifocal ventricular premature contractions and two episodes of ventricular tachycardia treated with intravenous lidocaine therapy The presence of pericarditis was described on the seventh and eighth hospital days. The patient was discharged after 14 days of hospitalization on procainamide ..0 mg. every 3 hours and coumadin therapy On Dec 19 19 4 the patient was readmitted to the same hospital because of recurrent syncopal episodes. Cardiomegaly and pulmonary râles were noted Treatment with digoxin and furosemide was instituted On the second hospital day the patient developed ventricular fibrillation which was successfully reverted with precordial shock and lidocaine therapy was again instituted On the following day recurrent ventricular tachycardia occurred and procainamide therapy was increased to .00 mg every 3 hours On the seventh hospital day multiple episodes of ventricular tachycardia were again observed The patient became hypotensive and was transferred to Strong Memorial Hospital

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Under local anesthesia intra aortic balloon counterpulsation was instituted via a right common femoral aortotomy with a 10 mm woven Dacron sidearm graft and an AVCO 40 mL balloon advanced under fluoroscopic control to a position below the transverse aortic arch (Fig 1) The patient's blood pressure and rhythm were stabilized on intra aortic balloon support and antiarrhythmic therapy *prior to* coronary angiography and left ventriculography *Angiographic* study showed a large aneurysm of the *anterior* and apical portion of the left ventricle with significant *mitral* regurgitation Multiple episodes of ventricular tachycardia *were* observed despite antiarrhythmic therapy and intra aortic balloon counterpulsation

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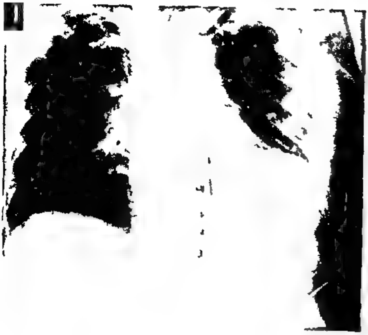

Fig 1 Chest x ray revealing left ventricular aneurysm

Twenty eight hours after admission the patient underwent left ventricular aneurysmectomy and mitral valve replacement At operation there was a large thin walled aneurysm of the left ventricle located over the anterior and lateral surfaces extending from the region of the septum to the anterolateral papillary muscle and from base to apex The area of infarction encompassed approximately 40 to 45 per cent of the left ventricle Both papillary muscles were involved in the area of infarction surrounding the aneurysm and moderate mitral incompetence was noted The left ventricular aneurysm was excised and the mitral valve was replaced with a Bjork Shiley 1328 prosthesis The patient s postoperative course was one of progressive deterioration with hypotension and low output state He died 12 hours after surgery

Pathologic findings

The resected myocardial aneurysm measured approximately 10 by 8 cm and varied from 1 to 5 mm in thickness There was evidence of healed infarction and marked fibrosis The section of the papillary muscles received with the resected valve showed organizing myocardial infarcts

At autopsy, the prosthetic mitral valve was secure and well placed Coronary artery examination revealed complete occlusion of the left anterior descending branch by marked atherosclerosis and recent thrombus, while the circumflex and right coronary arteries showed only moderate limitation of their lumina by atherosclerotic plaque There was residual healed and healing infarct in the upper septum and the anterior left ventricular wall There was a recent infarct in the lower portion of the septum which antedated the surgery by 1 to 2 days A dissecting aortic aneurysm was present in the wall of the thoracic aorta The hematoma in its major dissection extended from 2 cm below the origin of the left subclavian artery for 25 cm , approximately the length of the intra aortic balloon A narrow plane of dissection extended below to the origin of the left renal artery There was minor atherosclerotic plaque formation in the remainder of the aorta The origins of the renal arteries, celiac axis, and superior mesenteric arteries were patent There were no lacerations in the intimal surface of the aorta, so no point of entry for the dissection was identified

Microscopically the plane of the dissection bisected the media of the aorta (Fig 2) The media showed mild myxoid degeneration similar to that seen in older aortas There was no evidence of degenerative disease attributable to cystic medial necrosis, Marfan's syndrome or collagen vascular disease

Discussion

There is increasing evidence that patients in cardiogenic shock complicating acute myocardial infarction or cardiovascular surgery can be temporarily improved with institution of intra aortic balloon counterpulsation

The purpose of this communication is to describe a complication of intra aortic balloon pumping and to direct further attention to potential abnormalities of the wall of the aorta Optimum positioning of the balloon catheter for maximum diastolic augmentation is that position closest to the aortic valve The risk of cerebral embolization or trauma to aortic arch vessels however dictates that the balloon tip be at a point distal to the origin of the left subclavian artery This case report describes a dissecting aneurysm of the descending aorta adjacent to the position of the balloon catheter in the aorta without evidence of endothelial laceration There had been no difficulty with introduction of the balloon catheter and clinical symptoms or signs of dissection were not apparent

Local trauma to the wall of the aorta during balloon counterpulsation is uncommon Four cases of a dissection of the aorta have been described, but each differ somewhat from the case reported here

A case described by O Rourke and Shepherd[1] had a laceration in the wall of the aortic arch with a 10 cm dissecting aneurysm extending down the thoracic aorta The laceration in the aorta

Fig 2 Photomicrograph of wall of the aorta Arrows indicate media of the aorta bisected by the dissecting aneurysm Thrombus *(TH)* lies within plane of the dissection

described was 2 to 3 cm away from the tip of the balloon catheter

Dunkman and associates have described two cases of dissection of the aorta during insertion of the balloon catheter In one case the catheter entered the arterial wall and was completely within a false lumen In the second case the balloon catheter created a false lumen for 3 to 4 cm and then re entered the aortic lumen These complications therefore occurred during placement of the catheter and not secondary to use of the device with the catheter in the lumen of the aorta Finally the cooperative clinical trial of intra aortic balloon counterpulsation reported by Scheidt and associates mentioned one case of subadventitial hematoma with dissecting fusiform aneurysm No further details are given however as to the pathologic description or proposed mechanism of development of the aneurysm

Aortic dissection could result from catheter tip laceration (1) during implantation (2) during normal inflation deflation motion or (3) secondary to patient movement despite secure fixation of the catheter to the femoral artery

O Rourke and Shepherd have demonstrated in a cadaver study that the tip of the catheter can move in cephalad direction and possibly lacerate the aortic wall when the patient assumes the sitting position Thus they recommend that the tip of the balloon catheter be placed 4 cm below the top of the aortic knob and the position checked by chest x ray in the sitting position

In addition to catheter tip damage lateral wall pressure from balloon inflation could conceivably result in aortic wall damage The balloon size in relation to cross sectional area of the aorta must vary significantly between patients and therefore lateral wall pressure would be variable

Weber and Janicki[3] have determined that greatest augmentation of mean aortic root diastolic pressure occurs with complete occlusion of the aorta Considering the measurements of the midthoracic aorta available however it is unlikely that any commercially available balloons occlude the aorta Determination of the correct balloon size for maximum benefit and minimum risk in each individual patient is at best an estimation

There was no intimal tear evident in our case reported here Without any evidence of laceration of the aorta it is possible that lateral and shearing forces generated by the balloon could result in a dissection The length of the major dissection in our case was equivalent to the length of the balloon itself and suggests a local traumatic effect of balloon inflation Lastly the usual dissecting aortic aneurysm develops the plane of dissection in the outer media very close to the adventitia It is of interest that the plane of dissection in this case bisects the media suggesting that unusual factors contributed to the development of this aneurysm No evidence of unusual cystic medial degeneration could be found Thus aortic dissection and possible perforation must be considered even when correct balloon catheter position has been established

Summary

A 61 year old man with recent myocardial infarction complicated by a ventricular aneurysm and recurrent ventricular tachycardia underwent intra aortic balloon counterpulsation prior to angiography and left ventricular aneurysmectomy A dissecting aneurysm of the descending aorta adjacent to the position of the balloon catheter was found at autopsy No intimal tear or cystic medial degeneration of the aorta was present to account for the dissection The authors suggest that lateral and shearing forces generated by inflation of the balloon could result in dissection of the aorta

The authors wish to express their gratitude to Dr Paul N Yu for his review of the manuscript

REFERENCES

1. Dunkman W B Leinbach R C Buckley M J et al. Clinical and hemodynamic results of intraaortic balloon pumping and surgery for cardiogenic shock Circulation 46 465 1972
2. Weber K T and Janicki J S Intraaortic balloon counterpulsation A review of physiological principles, clinical results and device safety Ann Thorac Surg 17 602 1974
3. Scheidt S Wilner G Mueller H, et al. Intra aortic balloon counterpulsation in cardiogenic shock. Report of a cooperative clinical trial N Engl J Med 288 979 1973
4. O Rourke M F Chang V P Windsor H M et al Acute severe cardiac failure complicating myocardial infarction Experience with 100 patients referred for consideration of mechanical left ventricular assistance Br Heart J 37 169 1975
5. Kuhn L A Salvage with assisted circulation in acute myocardial infarction and shock Am J Cardiol. 34 873 1974
6. Cohen L A Current status of circulatory assist devices, Am J Cardiol 33 316 1974
7. O Rourke M F and Shepherd K M Protection of the aortic arch and subclavian artery during intraaortic balloon pumping J Thorac Cardiovasc Surg 65 543 1973
8. Weber K T, Janicki J S., and Walker A. A The influence of balloon volume and diameter on optimal intraaortic balloon assist (abst) Trans Am Soc. Artif Intern Organs 2 71 1973

Isolated dextroversion of the heart with asymmetric septal hypertrophy

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The commonest type of right thoracic heart is situs inversus in which thoracic and abdominal viscera are in mirror image positions.[1] Ninety to 95 per cent of such patients have hearts that are otherwise normal. A second type of right thoracic heart, dextroversion, is an uncommon anomaly characterized by situs solitus (normal position) of aorta, atria, lungs, and abdominal viscera but with persistent right thoracic cardiac apex. In contrast to situs inversus, patients with dextroversion almost invariably have additional cardiac malformations that occur singly or in combination.

Asymmetric septal hypertrophy (ASH) is now recognized as a relatively common genetic disease exhibiting a wide spectrum of clinical manifestations. The disorder is characterized by abnormal myofibrils in the interventricular septum with varying degrees of extension into the left ventricular anterior and posterior walls. The clinical expressions are believed to depend upon the extent and distribution of these abnormal cells. ASH typically occurs as an isolated cardiac disorder although occasional coexistence with congenital or acquired heart disease or with Friedreich's ataxia has been described.[4] The purpose of this report is to describe a patient born with uncomplicated *dextroversion of the heart* but presenting in the sixth decade with associated obstructive ASH. Insofar as we know, this combination is unique and results in pathophysiologic interactions that present stimulating challenges in clinical diagnosis. Accordingly, clinical, phonocardiographic, vectorcardiographic, echocardiographic, hemodynamic, angiographic, and electrophysiologic studies are described and analyzed in detail.

Case report

The patient, a 56-year-old white man, was referred to the Hospital of the University of Pennsylvania because of palpitations of 2 years' duration. Asymptomatic right thoracic heart had been recognized since childhood. An unimpressive intermittent murmur was commented upon at age 15, but at age 54 no murmur was mentioned. At age 55 hypertension was discovered and treated. At age 56, a loud systolic murmur was first described. The patient denied symptoms of congestive heart failure, chest pain, syncope, or presyncope. Palpitations occurred daily but bore no relation to exercise. There was no known family history of cardiac disease.

Physical examination revealed an acyanotic man with gastric tympany on the left and hepatic and cardiac dullness on the right (situs solitus of abdominal viscera with right thoracic heart). There were brisk carotid and brachial arterial upstrokes. A systolic thrill was isolated to the lower *right* sternal edge, and a conspicuous systolic impulse was present along the *right* sternal border. Both the first and second heart sounds were single, with the latter accentuated. A Grade 4/6 crescendo systolic murmur began after the first sound, extended to the second sound, and was audible over the entire right precordium. The murmur significantly decreased with squatting and increased with prompt standing. Isometric exercise (clenched fists) similarly decreased the intensity of the murmur.

The electrocardiogram (ECG) revealed sinus rhythm with occasional ventricular premature beats (Fig. 1). The P wave was broad and notched but the P axis was normal, appropriate for normal atrial situs. There was an equidiphasic R/S in V_1 while V_2 through V_6 had prominent R waves. Clearly evident Q waves were present in *left* precordial leads, indicating normal direction of septal depolarization. Right precordial

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Summary

A 61 year old man with recent myocardial infarction complicated by a ventricular aneurysm and recurrent ventricular tachycardia underwent intra aortic balloon counterpulsation prior to angiography and left ventricular aneurysmectomy A dissecting aneurysm of the descending aorta adjacent to the position of the balloon catheter was found at autopsy No intimal tear or cystic medial degeneration of the aorta was present to account for the dissection The authors suggest that lateral and shearing forces generated by inflation of the balloon could result in dissection of the aorta

The authors wish to express their gratitude to Dr Paul N Yu for his review of the manuscript

REFERENCES

1 Dunkman W B Leinbach R C Buckley M J et al Clinical and hemodynamic results of intraaortic balloon pumping and surgery for cardiogenic shock Circulation 46 465 1972
2 Weber K. T and Janicki J S Intraaortic balloon counterpulsation A review of physiological principles clinical results and device safety Ann Thorac Surg 17 602 1974
3 Scheidt S Wilner G Mueller H et al Intra aortic balloon counterpulsation in cardiogenic shock. Report of a cooperative clinical trial N Engl J Med 288 979 1973
4 O Rourke M F Chang V P Windsor H M et al. Acute severe cardiac failure complicating myocardial infarction Experience with 100 patients referred for *consideration of mechanical left ventricular assistance* Br Heart J 37 169 1975
5 Kuhn L. A Salvage with assisted circulation in acute myocardial infarction and shock, Am J Cardiol 34 873 1974
6 Cohen L A Current status of circulatory assist devices Am J Cardiol 33 316 1974
7 O Rourke M F and Shepherd K M Protection of the aortic arch and subclavian artery during intraaortic balloon pumping J Thorac Cardiovasc Surg 65 543 1973
8 Weber K T Janicki J S and Walker A A The influence of balloon volume and diameter on optimal intraaortic balloon assist (abst) Trans Am Soc Artif Intern Organs 2 71 1973

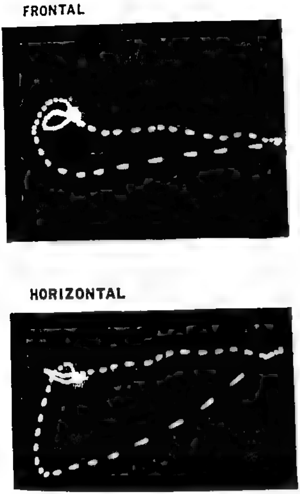

Fig 3 Frontal and horizontal plane vectorcardiogram demonstrating an anterior displaced loop with a large left maximum spatial vector compatible with dextroversion and left ventricular hypertrophy (1 cm = 1 mv dash time = 2 5 msec and the blunt end of the teardrop is the leading edge)

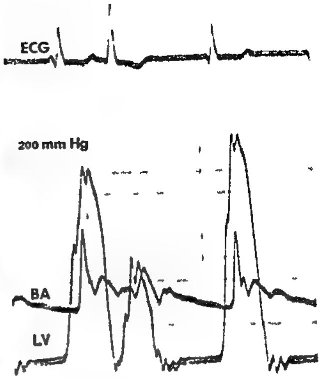

Fig 4 Simultaneous brachial arterial (BA) and left ventricular (LV) pressure pulses demonstrating a left ventricular outflow gradient and the typical brisk upstroke and peaked brachial pulse of obstructive asymmetric septal hypertrophy Note that the post premature beat (third complex) exhibits a decreased pulse pressure and an increased gradient

but revealed the coronary arterial anatomy of dextroversion without ventricular inversion Left ventriculogram confirmed the connection of an anatomic left ventricle to the aorta

Electrophysiologic studies provided the following information intracardiac conduction times and refractoriness were evaluated with pacing and the extrastimulus method The intracardiac recordings, simultaneous ECG Leads I II III, and V and time lines generated at 10 and 100 msec were displayed on a multichannel oscilloscope and stored on magnetic tape for subsequent analysis. Sinus node function as determined by postpacing and post APC suppression time was normal (112 per cent of the basic sinus cycle length) A short PR interval was present (120 msec) as well as an intra atrial conduction defect. Intra atrial mapping demonstrated a delay in left atrial activation as measured from the coronary sinus. Conduction time from the high right atrial (HRA) electrogram to the coronary sinus was 105 msec (normal 70 ± 10 msec). The HRA electrogram occurred 25 msec *prior* to the onset of the surface P wave and the atrial electrogram in the His bundle electrogram occurred at the onset of the P wave Atrioventricular nodal and His Purkinje conduction times were normal (AH = 90 HV = 45) (Fig. 6) No evidence of preexcitation was detected during sinus rhythm or during pacing. At a basic paced cycle length of 600 msec the effective refractory period of the atrium was 260 msec while the functional and effective refractory periods of the AV node were 345 and less than 260 msec respectively These values are all within normal limits. Spontaneous APC s and VPC s were recorded during the study and APCs at coupling intervals of 280 to 315 msec produced extra beats due to sinus node reentry

Discussion

Dextroversion as an isolated malposition without complicating cardiac malformations appears to have no physiologic significance However in approximately 90 per cent of cases of dextroversion intracardiac anomalies coexist These typically include congenitally corrected transposition of the great arteries pulmonic stenosis hypoplasia of the pulmonary artery and ventricular or

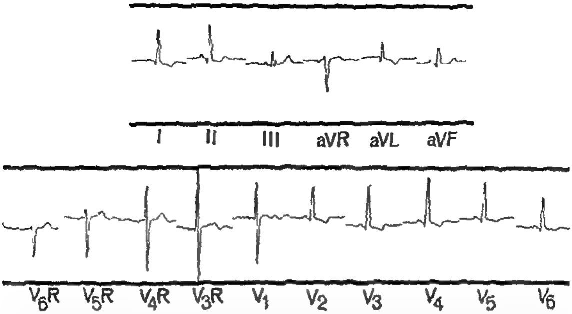

Fig 1 Standard 12 lead ECG with the addition of right precordial leads showing prominent R waves in the left precordial leads and the development of an rS pattern in the V_4R position compatible with dextroversion and isolated left ventricular hypertrophy Note the Q waves in the left precordial leads and their absence in the V R position confirming left to right septal depolarization and indicating noninversion of the ventricles The PR interval is short and the P wave notched

Fig 2 Posterior anterior chest roentgenogram showing a left aortic arch left descending aorta and left stomach but a right thoracic heart

leads showed the development of an rS pattern in the V R position but no Q waves confirming left to right septal depolarization and noninversion of the ventricles Twenty four hour ECG monitoring recorded only frequent periods of unifocal ventricular premature beats greater than 20 per hour and rare junctional premature beats

The chest x ray (Fig 2) showed a left aortic arch a left descending aorta a left sided stomach but a right thoracic heart

The echocardiogram suggested systolic anterior motion of an atrioventricular valve The septum was not well visualized

The vectorcardiogram (Fig 3) was abnormal due to initial rightward and posterior forces an anterior displaced loop and a large left maximum spatial vector indicating left ventricular hypertrophy The inscription of the horizontal loop was consistent with dextroversion and left ventricular hypertrophy (Fig 3)

The indirect carotid arterial tracing showed a brisk upstroke with double systolic peaks The phonocardiogram recorded a crescendo systolic murmur but neither a third nor a fourth heart sound The second sound was single

Cardiac catheterization and coronary cineangiography revealed the following The brachial arterial pressure was 132/72 mm Hg with a mean of 92 the pulse was characteristically brisk and double peaked The pressure in the body of the left ventricle was 230/10 mm Hg and in the left ventricular outflow tract 132/10 mm Hg resulting in a peak gradient of 92 mm Hg During the course of the study the gradient varied from 20 to approximately 100 mm Hg (Figs 4 and 5) Amyl nitrite was inhaled but ventricular premature beats prevented analysis of the hemodynamic response The maximal postpremature beat left ventricular to aortic gradient was 130 mm Hg and the brachial arterial pulse pressure typically decreased (Fig 4) On right heart catheterization the pulmonary capillary wedge pressure was 11 mm Hg the pulmonary artery pressure 25/12 with a mean of 16 the right ventricular pressure 25/5 and the right atrial mean pressure 4 mm Hg The green dye cardiac output and index was 3 1 L per minute and 1 5 L per minute per square meter Coronary arteriograms showed no intraluminal narrowing

continuity with the anterior mitral leaflet. Such was the case in our patient. It was unusual that neither presystolic distension of the anterior left ventricle nor a fourth heart sound was present, findings which are the rule in patients with obstructive ASH.[3]

Obstructive and nonobstructive ASH rarely have associated congenital cardiac anomalies. Several reports based upon clinical and angiographic criteria have described the coexistence of obstructive ASH in both primum[7] and secundum atrial septal defects,[8, 9] common A-V orifice with pulmonic stenosis,[9] valvular aortic stenosis, and mirror-image dextrocardia.[4]

The electrocardiographic-electrophysiologic information in this patient were noteworthy for a number of reasons. First, the surface ECG showed an intermittent short PR interval and an intraventricular conduction defect. In the review by Braunwald and associates[1] of idiopathic hypertrophic subaortic stenosis, 5 per cent exhibited the Wolff-Parkinson-White complex and 11 per cent had part of the ECG diagnosis, i.e., either short PR interval or delta wave. Our patient demonstrated a short PR on the surface ECG but *intracardiac* electrograms revealed no evidence of pre-excitation and all conduction times were normal. Intracardiac recordings revealed atrial activity *preceding* the surface P wave, thus the surface PR interval was falsely short. The probable explanation of this was that initial atrial depolarization generated from the posterior right atrium (as occurs in dextroversion) was isoelectric and thus not represented on the surface ECG. Although this phenomenon was noted by Scharf and colleagues in a few patients, none demonstrated this degree of prematurity of the high atrial electrogram. Furthermore, a left atrial abnormality as defined by Scharf and associates[13] was noted, a finding consistent with a P wave that was 100 msec in duration and markedly notched.

Summary

Dextroversion of the heart is an uncommon congenital anomaly characterized by situs solitus (normal position) of thoracic and abdominal viscera with right cardiac apex. *Isolated* dextroversion, i.e., *without* associated congenital heart disease, is rare but its occurrence permits adult survival, setting the stage for late development of acquired heart disease. The patient herein reported was known since childhood to have a right thoracic heart that represented isolated uncomplicated dextroversion. He presented in the sixth decade with a new murmur that proved to be due to asymmetric septal hypertrophy (ASH) with obstruction. This combination of anomalies is possible only if dextroversion exists *without* ventricular inversion, since aortic-anterior mitral leaflet continuity is obligatory for obstructive ASH. This paper presented clinical, phonocardiographic, vectorcardiographic, echocardiographic, hemodynamic, angiocardiographic, and intracardiac electrophysiologic information on the unique combination of isolated dextroversion of the

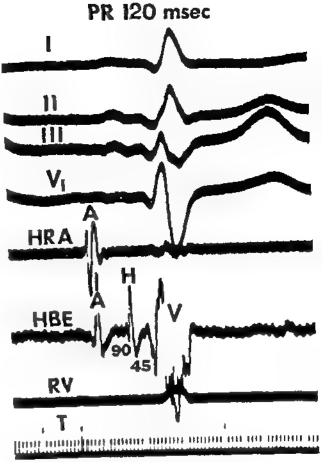

Fig. 6. From top to bottom are ECG Leads I, II, III, and V_1, high right atrial electrogram (HRA), His bundle electrogram (HBE), right ventricular electrogram (RV), and time lines (T) at 10 and 100 msec. Note that the P wave is notched and the PR interval is short but the onset of atrial activity (A) in the HRA precedes the surface P wave activity by 25 msec. Intracardiac conduction times are normal (AH = 90 msec, HV = 45 msec.)

Fig 5 Pressure pulses generated during slow withdrawal of an Eppendorf catheter from the left ventricular (LV) body to the aorta The subvalvular chamber is characteristic of obstructive asymmetric septal hypertrophy

atrial septal defect[1] It is unclear why the embryologic bulboventricular loop fails to rotate leftward, leaving a right cardiac apex No familial transmission has been identified in dextroversion

The patient described in this report was known to have a right thoracic heart since childhood however no associated heart disease was recognized until his fifth decade The development of symptomatic premature ventricular contractions prompted a physical examination that detected a new loud systolic murmur The configuration of the murmur implied two sources a crescendo decrescendo midsystolic murmur of left ventricular outflow obstruction and a crescendo late systolic murmur of mitral regurgitation The responses to squatting prompt standing and isometric exercise were in accord with dynamic left ventricular outflow obstruction Electro and vectorcardiography revealed patterns atypical for isolated dextroversion, i e , increased *left* precordial voltage reflecting marked isolated *left* ventricular hypertrophy (LVH) Congenital anomalies commonly associated with dextroversion (see above) produce right ventricular hypertrophy either alone or in combination with left ventricular hypertrophy so that the dominant ECG forces remain over the right thorax The presence of dominant electrical forces in the *left* precordium (Figs 1 and 3) indicated a coexisting lesion producing *isolated* LVH In dextroversion without congenitally corrected transposition, the anterior ventricle is anatomically a left ventricle and the right thoracic apical ventricle anatomically right, resulting in normal left to right septal depolarization Q waves in the left precordium and absent Q waves in the right precordium in our patient were in accord with noninverted ventricles Accordingly the prominent sustained impulse from the anterior ventricle (anatomically left ventricle) was consistent with the ECG diagnosis of isolated LVH We were unable to obtain an echocardiogram of satisfactory diagnostic quality although late systolic anterior motion of the anterior leaflet of an atrioventricular valve was believed to be present At cardiac catheterization a left ventricular aortic gradient was recorded (20 to 100 mm Hg) with a subvalvular chamber (Fig 5) After a premature ventricular beat the gradient rose to 130 mm Hg while the systemic arterial pulse pressure fell Other features of obstructive ASH included angiographic systolic apposition of the anterior mitral leaflet and the interventricular septum a small end systolic left ventricular volume associated with hypertrophy of the papillary muscles and 3+ (out of 4) mitral regurgitation Cineangiography revealed that the right atrium was posterior and connected to an anatomic right ventricle The right ventricle occupied the right thoracic apex and the left ventricle was anterior and connected to an anterior aorta It is noteworthy that in the setting of dextroversion obstructive ASH could *only* occur in the *absence* of ventricular inversion i e an anatomic left ventricle must connect to the aorta which must *maintain*

Clinical pathologic conference

Colin Ogilvie M D F R C P
J M Kay M D M R C Path
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Liverpool, England

Prof Heath An 89 year old woman was admitted to hospital as an emergency case on April 7 1971 having fallen down at home She complained of pain in the right hip She had suffered from rheumatic fever during childhood On examination the patient was pale and rather confused The right hip was tender swollen and painful to move There was external rotation and shortening of the right leg Both ankles showed pitting edema but there was no elevation of the jugular venous pressure The pulse rate was about [illegible] per minute with atrial fibrillation and the systemic blood pressure was 160/115 mm Hg The apex beat was located in the fifth left intercostal space 8 cm from the midline and the cardiac impulse was tapping in character A systolic thrill was palpable over the cardiac apex Auscultation revealed a loud first sound in the mitral area A Grade 3 pansystolic murmur and a Grade I mid diastolic murmur were audible at the apex of the heart and the systolic murmur was conducted to the axilla Auscultation of the chest revealed coarse rhonchi throughout all lung fields together with fine crepitations at the lung bases The abdomen was normal and no abnormalities were found in the nervous system Various investigations were carried out and the patient was treated conservatively for [illegible] days until a surgical operation was performed The patient became drowsy and although she could move both arms and legs there appeared to be some weakness of the left arm and the left side of the face All the tendon reflexes were present and appeared to be equal The plantar reflexes were equivocal After the operation the patient's level of consciousness varied from day to day and she suffered from recurrent attacks of severe breathlessness and wheezing together with a cough productive of abundant frothy sputum There was edema of the chest wall and sacrum Crepitations were audible at both lung bases Despite further medical treatment the patient's condition gradually deteriorated and she died on April 23 1971

Investigations The levels of hemoglobin (in grams per 100 ml) packed cell volume (per cent) and mean corpuscular hemoglobin concentrations (per cent) were as follows on April 8 1971 9 6 Gm per 100 ml 30 per cent 33 per cent on April 14 11.3 Gm per 100 ml 34 per cent 33 per cent The white cell count per cubic millimeter was 6 200 on April 8 and 8 600 on April 14

Dr Ogilvie Nowadays it is not uncommon to admit patients of this advanced age to hospital so one is becoming more familiar with diseases of the aged It is clear that this old lady fell and broke her leg and more specifically fractured the neck of her right femur The operation she had some days later was likely to have been pinning and plating of the fractured bone (*A radiograph of the pelvis was shown*) This radiograph confirms that she had such a fracture I see no evidence of intrinsic bone disease in this radiograph to account for the injury although we realize that old women are more prone than men to osteoporosis

I am intrigued by the fact that one of the few items of history given in this sparse clinical summary occurred in the last century We are told that she had rheumatic fever in her childhood This must have been at the time when Gladstone was Prime Minister of Great Britain and Cleveland was President of the United States of America At first sight therefore one is not surprised to find that with a history of rheumatic fever she now has clinical signs of mitral incompetence However on reflection I doubt very much that mitral regurgitation of this magnitude with such an obvious murmur and thrill has existed for 80 years although of course the loudness of a murmur does not necessarily reflect the

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heart with obstructive asymmetric septal hypertrophy

REFERENCES

1 Perloff J K The clinical recognition of congenital heart disease Philadelphia 1970 W B Saunders Company
2 Clark C E Henry W L and Epstein S E Familial prevalence and genetic transmission of idiopathic hypertrophic sub aortic stenosis N Engl J Med 289 709 1973
3 Epstein S E Henry W L Clark C E Roberts W C Maron B J Ferrans V J Redwood D R and Morrow A G Asymmetric septal hypertrophy Ann Intern Med 81 650 1974
4 Parker D P Kaplan M A and Connolly J E Coexistent aortic valvular and functional hypertrophic sub aortic stenosis Am J Cardiol 24 307 1969
5 Johnson A D Lonky S A and Carleton R A Combined hypertrophic sub aortic stenosis and calcific aortic valvular stenosis Am J Cardiol 35 706 1975
6 Smith E R Flemington C S Hefferman L P and Sangalang V E Asymmetric septal hypertrophy The cardiomyopathy of Friedreich s ataxia Clin Res 23 208A 1975
7 Adad W A Pietras R J and Bliss H A Left ventricular outflow tract obstruction with an ostium primum defect Arch Intern Med 125 701 1970
8 King S M Vogel J H K and Blount S G Idiopathic muscular subvalvular aortic stenosis with associated congenital cardiovascular lesions Am J Cardiol 15 837 1965
9 Forker A D and Morgan J R Hypertrophic sub-aortic stenosis with ostium secundum atrial septal defect Chest 60 512 1971
10 Moethan M E Paul M H and Lev J M Common AV orifice with pulmonary valvular and hypertrophic sub aortic stenosis Am J Cardiol 10 291 1962
11 Cochran P T and Wanamaker J L Idiopathic hypertrophic sub aortic stenosis in a patient with mirror image dextrocardia Chest 67 1 1975
12 Braunwald E Lambrew C T Rockoff S D Ross J Jr and Morrow A G Idiopathic hypertrophic sub-aortic stenosis Description of the disease based upon an analysis of 64 patients Circulation 29 (Suppl IV) 1 1964
13 Scharf D L Kastor J A and Goldreyer B N Catheter mapping of human atrial endocardial activation Circulation 49 50(Suppl III) 81 1974

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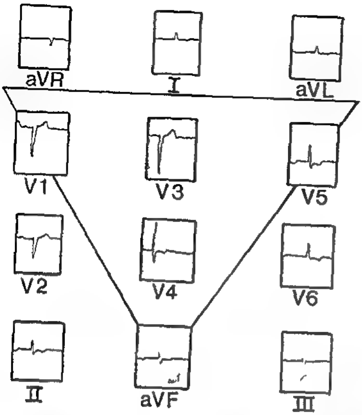

Fig 1 ECG taken on April 8 1971

Fig 2 Chest radiograph taken on April 8 1971 There is a curved opacity (arrow) within the heart shadow

degree of mitral reflux I suspect that in spite of the history of rheumatic fever we have to be on the lookout in this case for another cause of mitral incompetence which has developed much more recently I am intrigued by the fact that she still has a loud first sound with a tapping apical impulse which suggests to me that she still ha some mobility of the cusps of her mitral valve This does not seem very much like uncomplicated rheumatic heart disease although I appreciate that occasionally one still hears a loud first mitral sound in rheumatic mitral incompetence if the aortic cusp of the mitral valve has remained mobile What concerns me too is the fact that if she had rheumatic mitral incompetence for 80 years we should have considerably more evidence of left ventricular hypertrophy than is evident from the clinical description

I should like to see an electrocardiogram (ECG) (*One carried out on April 8 was shown*) This confirms the presence of controlled atrial fibrillation (Fig 1) and I note there are ischemic changes over the left ventricular leads There is some slurring of the QRS complexes but I would not take too much notice of that in a woman of this age There are no P waves due to the atrial fibrillation and so it is not possible to comment on atrioventricular conduction

May I see a radiograph of the chest? (*An AP radiograph of the chest taken on April 8 was shown*) This radiograph shows generalized cardiac enlargement with dilatation of the left atrium There are changes in the lung fields including increased vascularity of the upper zones, consistent with pulmonary venous and arterial hypertension due to mitral disease What is unexpected is an opacity in the area of the heart shadow (Fig 2) I appreciate that a full cardiac investigation was not carried out on this old person admitted as an emergency for a fractured femur but I must point out that the absence of lateral films makes the positioning of the lesion causing this radiological opacity very difficult It is certainly dense enough to be an area of calcification but its shape is very irregular

Prof Heath It may not be as irregular as you think I am led to understand that the shape of this opacity is so characteristic as to be almost pathognomonic of a certain disease Radiologists regard this peculiar shape as being in the form of an inverted J or an inverted C Does that ring a bell?

Dr Ogilvie Not in my ears I am not too certain as to the precise relation of this area of calcification to cardiac anatomy assuming that it is in the heart at all it could be endocardial or myocardial or even calcification in a thrombus within a cardiac chamber As I said previously I

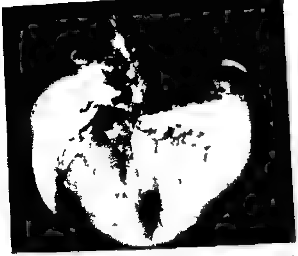

Fig 3 Postmortem radiograph taken after dissection and fixation of the heart in formalin There is massive calcification of the posterior aspect of the mitral valve annulus The calcified tissue was divided into two fragments when the heart was opened at necropsy There is also patchy calcification of the interventricular and circumflex branches of the left coronary artery

Fig 4 The heart has been opened to display the mitral valve with its anterior and posterior leaflets situated on the left and right hand sides of the picture respectively The anterior leaflet is normal for a subject of this age and its chordae are elongated and thin There is massive calcification of the annulus which has elevated the posterior leaflet toward the left atrial cavity The leaflet is held taut and curved over the edge of the calcified annulus by the tense chordae The left atrial endocardium shows numerous tiny gray nodules of amyloid

think the mitral incompetence in this elderly woman is of comparatively recent onset and I was considering from the clinical story that it might be related to infection of the mitral valve by bacterial endocarditis or even rupture of a papillary muscle but having seen the calcification in relation to the heart I can see I must try to relate the regurgitation to that

With regard to the cerebral incident the transient weakness of the left arm and left side of the face together with a fluctuating level of consciousness in a patient who has fallen should make us think of a subdural hematoma frontoparietal in site However in this 89 year old woman it could be anything thrombosis embolism from the left atrium or cerebral hemorrhage I think the lesion was too transient for hemorrhage and too late after the injury for fat embolism The last part of the story indicates that the patient died in congestive cardiac failure both left and right

Prof Gray I think there is slurring of the QRS complexes and I wonder if this indicates some disturbance of conduction

Mr Ward It would be of interest to know the serum calcium level in this case for she may have had some bone disease predisposing to cardiac calcification

Prof Heath It was 8 6 mg per 100 ml

Dr Ogilvie That is a helpful negative finding

Dr Connor Was there any evidence of endocarditis? In particular did she have a pyrexia? Were blood cultures done? Was the erythrocyte sedimentation rate (ESR) raised?

Prof Heath She was apyrexial and blood cultures were not carried out The ESR (Westergren) was 10 mm in 1 hour

Dr Kenyon Do you not think that the opacity in the chest radiograph is cusplike suggesting that calcification is occurring in the mitral valve itself rather than in the myocardium?

Dr Ogilvie It seems to me that the calcification is more extensive than could be accounted for by its being confined to the cusps themselves

Dr Kay The right femur showed a pertrochanteric fracture which had been well fixed with a pin and plate There was evidence of chronic congestive cardiac failure with pitting edema of the legs and back bilateral pleural effusions and chronic venous congestion of the spleen and liver The heart showed two independent conditions both of which are known to cause cardiac failure in elderly people One of these conditions affected the mitral valve and the other affected the myocardium and endocardium The heart (46

Fig 5 Section showing posterior wall of left atrium (*a*) posterior leaflet of mitral valve (arrow) and posterior wall of left ventricle (*V*) The annulus fibrosus and adjacent ventricular myocardium are replaced by enormous amorphous masses of calcific material (*C*) which protrude anteriorly into the ventricular cavity along the inferior surface of the mitral valve leaflet (arrow) which shows slight fibrous thickening consistent with age change (Hematoxylin and eosin stain × 3 75)

Fig 6 Posterior wall of left atrium showing an irregular dark staining amorphous acellular nodule of amyloid which is located in the subendocardial connective tissue and which elevates the endocardium (Sirius red stain × 360)

Gm) was enlarged due to hypertrophy of both the right and left ventricles The free wall of the right ventricle weighed 75 Gm and the weight of the left ventricle together with the interventricular septum was 270 Gm The right ventricle normally weighs less than 65 Gm and the left ventricle less than 190 Gm [1] The anterior leaflet of the mitral valve was not thickened and its chordae was elongated and thin There was no fusion of the commissures and the appearances did not suggest chronic rheumatic disease There was massive calcification of the posterior aspect of the annulus fibrosus of the mitral valve which was well demonstrated in a postmortem radiograph of the heart (Fig 3) The calcific tissue was cylindrical in shape and its maximum diameter was 3 cm Short spicules of calcification extended downward from the annulus into the underlying left ventricular myocardium This massive calcification of the mitral valve annulus (Fig 4) produced the characteristic curved opacity which overlay the cardiac shadow in the chest radiographs taken during life (Fig 2) The calcified annulus had elevated the posterior leaflet toward the left atrial cavity The leaflet was taut and curved downward over the edge of the calcified ring being held fixed in this position by the tense chordae (Fig 4) The elevation and fixation of the posterior leaflet are the major anatomical factors causing mitral incompetence in this disease In a histological section the posterior leaflet was seen to be thin and stretched over the massively calcified annulus which bulged forward into the atrioventricular canal (Fig 5) Sometimes in this disease the enlarged calcified annulus projects so far into the mitral valve orifice that it causes mitral stenosis This did not appear to be present in this case since the circumference of the mitral valve was 10 cm The appearances are those of a condition known as *massive calcification of the mitral valve annulus* which is a significant cause of mitral incompetence and mitral stenosis in elderly women The first detailed description was given by Korn DeSanctis and Sell in 1962 [2] They described 14 cases occurring in women aged between 56 and 88 years The etiology is unknown but it is probably a degenerative disease and an exaggeration of the normal aging process It is apparently not related to rheumatic heart disease or rheumatoid disease

The left atrial endocardium showed numerous gray nodules measuring 1 mm in diameter When submerged in Lugol s iodine solution and then

washed in water these nodules displayed a mahogany brown color which is diagnostic of amyloid. This gray nodulation of the left atrial endocardium is characteristic of a condition known as *senile cardiac amyloidosis* which is a common condition in the elderly being found in about 23 per cent of necropsies in patients over the age of 80[3] Histologically these amorphous subendocardial deposits of amyloid were stained by Sirius red (Fig 6) and exhibited anomalous color birefringence or dichroism when such sections were examined in the polarizing microscope Extensive amyloid deposits were also present in the left atrial and left ventricular myocardium where extracellular amorphous eosinophilic material surrounded atrophic muscle cells. Small deposits of amyloid are encountered in other tissues in about a third of cases of senile cardiac amyloidosis This patient had such deposits in the walls of blood vessels in the pancreas liver adrenal and right breast In the lung amyloid infiltration was detected in the tunica media of muscular pulmonary arteries and in the alveolar walls

I conclude that this patient s congestive cardiac failure was due to a combination of senile cardiac amyloidosis and massive calcification of the mitral valve annulus which caused mitral incompetence The neurological symptoms and signs which first appeared 11 days before death were attributable to a hemorrhagic infarct (6 by 9 cm) which involved the cortex and white matter of the temporoparietal region of the right cerebral hemisphere and which was due to occlusive atheromatous disease of the cerebral arteries

PROF HEATH It is necessary to point out here that calcification of the mitral annulus is not an esoteric condition but is a common form of heart disease in the aged Pomerance has commented on the fact that this syndrome of mitral incompetence in the very old patient with a distinct underlying pathology has received scant attention in British textbooks of cardiology and pathology and scarcely more in monographs on cardiac pathology Series of cases have now been reported from the United States[2] and Great Britain

Similarly the other disease found at necropsy in this case by Dr Kay amyloidosis is a very common condition in the aged heart Cardiac amyloidosis has been found in 50 per cent of patients over 90 years[3, 6]

The collection of features that Dr Ogilvie has interpreted for us today constitutes a clinical picture that is in keeping with senile calcification of the mitral annulus Most of the cases[2] have presented as mitral incompetence developing in elderly patients with a mitral systolic murmur atrial fibrillation systemic hypertension and left ventricular hypertrophy Several have had cerebral infarction and in the literature there is frequent reference to conduction defects alluded to earlier by Professor Gray

One of the most characteristic features of the syndrome is the presence of an opacity in the chest radiograph in the form of an inverted J or C This characteristic shape is due to the fact that the calcification occurs only in the posterior part of the annulus related to the posterior cusp of the mitral valve There is a gap in the calcification in the anterior aspect of the annulus

An interesting Editorial which appeared in the *New England Journal of Medicine* pointed out that calcification and indeed bone formation is the natural course of events in the aortic valve of the ox[7] Why should calcification and ossification occur in the aortic valve in this species but in the mitral valve in man?

DR KAY I think that one of the interesting features about massive calcification of the mitral valve annulus is that it is for all intents and purposes a disease of women whereas calcific disease of the aortic valve has an over all male predominance As for the ox I do not know the answer to that problem

DR OGILVIE Now that it has become clear that the calcification was in the annulus and related only to the posterior cusp of the mitral valve we can understand the auscultatory signs Thus as I pointed out earlier in the face of a very loud mitral systolic murmur she still had a tapping apical impulse and a loud first sound in the mitral area This fits in very well with the fact that the anterior mitral cusp was mobile In chronic rheumatic heart disease where both cusps are rigid the first sound is blunted

DR. KAY You are quite right In this disease the calcification is entirely confined to the posterior part of the annulus

PROF HEATH It is perhaps of interest to recall that Prof Gray thinks that in this patient there was some slurring of QRS complexes indicative of some defect in conduction Spread of calcification from the mitral annulus into the myocardium and amyloidosis have both been commonly reported as leading to such an ECG change

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Fundamentals of clinical cardiology

The pathogenesis of the two forms of hypertensive pulmonary vascular disease

Grover M. Hutchins, M.D.
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Autopsy observations suggested that two morphologically distinct forms of hypertensive pulmonary vascular disease (HPVD) could be identified. The arterial type of HPVD was associated with conditions such as ventricular septal defects or patent ductus arteriosus which cause an elevation of pulmonary artery pressure without affecting venous pressure. The characteristic morphologic change in arterial HPVD appeared to be a progressive intimal cell proliferation in arterioles. In contrast, the venous form of HPVD was seen with left sided congestive heart failure (LCHF) caused by conditions such as mitral stenosis or myocardial infarction in which pressure is elevated throughout the pulmonary vascular bed. The characteristic morphologic change in venous HPVD appeared to be an intimal fibroelastosis (IFE) involving both veins and arteries.

This study was undertaken to investigate the impressions of progressive intimal changes in arterioles in arterial HPVD and of progressive venous and arterial IFE in venous HPVD. Patients with catheterization proved pulmonary hypertension and autopsy demonstrated lesions which would produce either elevation of arterial pressure only or LCHF with both venous and arterial hypertension were reviewed. Patients with proved pulmonary hypertension for which no cause could be found at autopsy, idiopathic pulmonary hypertension (IPH), were also studied. The results show a good correlation between the successive grades of the two forms of HPVD and the duration and severity of pulmonary hypertension.

Materials and methods

Patients were selected from the autopsy files of The Johns Hopkins Hospital in whom a clinical diagnosis of pulmonary hypertension had been established by cardiac catheterization. Fifty patients had an autopsy proved cardiovascular malformation, either a ventricular septal defect or patent ductus arteriosus, which would result in elevation of blood pressure in the main pulmonary artery. Fifty other patients were chosen in whom there was an autopsy demonstrated lesion in the left heart, mitral stenosis or myocardial infarction, which would lead to elevation of pulmonary venous pressure. The 15 patients with proved pulmonary hypertension for which no explanation was found at autopsy were also studied. No patient under 1 year of age was included in this study.

In the 115 patients the clinical record was studied to determine the duration of the pulmonary hypertension. In those with congenital malformations or IPH, age was considered equal to duration. The duration of venous HPVD was considered to be the time from first onset of symptoms of LCHF. Severity of pulmonary hypertension was determined from the catheterization records using the highest recorded systolic pressure. The interval from catheterization to death varied, however.

Slides stained with hematoxylin and eosin and with the Verhoeff-van Gieson elastic method taken from at least two areas of the lung were examined for each patient. The sections were reviewed several times without knowledge of the

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DR OGILVIE With the greatest of respect, I would not attach any significance to slight slurring of the QRS complexes in a woman of 89 years

DIAGNOSIS Massive calcification of the mitral annulus, senile cardiac amyloidosis

We are greatful to Mr G V Osborne Consultant Orthopaedic Surgeon and Mr S R Barter H M Coroner to the City of Liverpool for permission to publish details of this case

REFERENCES

1. Fulton R M Hutchinson E C and Jones A M Ventricular weight in cardiac hypertrophy Br Heart J **14** 413 1952
2. Korn D DeSanctis R W and Sell S Massive calcification of the mitral annulus N Engl J Med **267** 900 1962
3. Pomerance A The pathology of senile cardiac amyloidosis J Pathol Bacteriol **91** 357 1966
4. Pomerance A Pathological and clinical study of calcification of the mitral valve ring J Clin Pathol **23** 354 1970
5. Kirk R S and Russell J G B Subvalvular calcification of mitral valve Br Heart J **31** 684 1969
6. Pomerance A Senile cardiac amyloidosis Br Heart J **27** 711 1965
7. Editorial Os cordis N Engl J Med **267** 941 1962

Fig. 1. Grade A1 with intimal cell proliferation in arteriole but normal intima in parent trunk. (Hematoxylin and eosin ×300.)

Fig. 2. Grade A2 with early glomoid lesion in arteriolar lumen. The parent vessel has a normal intima. (Hematoxylin and eosin ×200.)

Fig. 3. Grade A3 with a typical glomoid in the arteriolar lumen. Markedly dilated postglomoid precapillary vessels form an angiomatoid. The parent artery at the bottom shows intimal fibroelastosis. The capillaries and veins are normal. (Hematoxylin and eosin ×[illegible]5.)

Fig. 4. Grade A4 with necrosis and acute inflammation in the wall and lumenal thrombosis of the artery proximal to arterioles containing advanced glomoid lesions. (Hematoxylin and eosin ×40.)

Table I Histological characteristics of the grades of the two forms of HPVD

Arterial HPVD
- A1—Arteriolar intimal cell proliferation
- A2—Early glomoid formation
- A3—Glomoid enlargement and postglomoid angiomatoid
- A4—Preglomoid hypertensive arterial necrosis

Venous HPVD
- V1—Arterial intimal cell proliferation
- V2—Arterial IFE and venous intimal cell proliferation
- V3—Arterial and venous IFE
- V4—Hypertensive arterial necrosis

Table II Average and range of duration and severity of pulmonary hypertension in arterial HPVD

	Histological grade			
	A1	*A2*	*A3*	*A4*
No of patients	17	10	18	5
Duration as age in years	4 (1 8)	6 (1 15)	18 (3 35)	20 (11 33)
Systolic pressure (mm Hg)	77 (41 118)	86 (61 115)	98 (44 130)	110 (100 130)

Table III Average and range of duration of LCHF and severity of pulmonary hypertension in venous HPVD

	Histological grades			
	V1	*V2*	*V3*	*V4*
No of patients	4	25	20	1
Duration of LCHF in years	1 (½ 1)	3 (½ 9)	10 (1 34)	8
Systolic pressure (mm Hg)	58 (29 103)	55 (30 92)	77 (31 160)	77

Table IV Average and range of age and severity of pulmonary hypertension in IPH

	Histological grade			
	A1	*A2*	*A3*	*A4*
No of patients	0	2	11	2
Duration as age in years		19 (5 32)	17 (1 35)	35 (32 38)
Systolic pressure (mm Hg)		95 (54 136)	118 (82 182)	132 (120 144)

patient s clinical findings and a grading system was devised Increasing steps in the grades appeared to reflect the progression of hypertensive changes and were based on qualitative histologic features in the intima (Table I)

In arterial HPVD *progressive intimal proliferation* in arterioles at their origin is the central feature (Figs 1 to 4) In grade A1 the intimal cell proliferation and consequent lumenal narrowing is present Progressive intimal cell proliferation and formation of multiple small channels create a glomoid in stage A2 Subsequent progression of the glomoid is seen and the appearance of dilatation of the postglomoid vessels characterizes stage A3 This cluster of dilated precapillary arterioles arising from the glomoid is called an angiomatoid In grade A4 there is necrosis of the preglomoid vessels

In venous HPVD the grading system is based on progression of IFE in arteries and veins (Figs 5 to 8) Glomoids and angiomatoids are not found in venous HPVD In grade V1 cellular intimal proliferation without the formation of new elastic fibers, is found in arteries and veins The appearance of elastic fibers in the proliferated arterial intima defines grade V2 In the next grade V3, the arterial IFE has progressed and IFE is also found in the veins Grade V4 is characterized by necrosis of arterial walls Arteries and veins of about 100 µ diameter are the most useful to evaluate An elastic stain is essential to grade venous HPVD lesions

Results

The lung slides from each patient were evaluated by the above system (Table I) and assigned a type and grade of HPVD It was found that all patients with congenital malformations producing an elevation of pulmonary arterial pressure without elevating pulmonary venous pressure and all patients with IPH had arterial type HPVD lesions All patients with LCHF had venous type HPVD lesions No admixture of the two forms of HPVD was observed

The comparison of the grade of arterial HPVD to the duration and severity of pulmonary arterial hypertension is shown in Table II There is a general correlation of increasing age and greater systolic pressure with a more severe grade of arterial HPVD although considerable varia

tion exists between individual patients Hypertensive necrotizing arteritis (A4) is seen only with long survival and severe elevation of pulmonary artery pressure

Table III shows the correlation of the grade of venous HPVD assigned to each patient and the duration and severity of LCHF The trend is for higher grades of morphologic change to be associated with higher systolic pressures and longer survival in left sided congestive heart failure Only one patient with necrotizing arteritis was observed In this case congenital mitral stenosis was responsible for LCHF

Patients with IPH all had arterial HPVD lesions of grade A2 or greater (Table IV) Pulmonary arterial pressure showed a good correlation with severity of HPVD but the patients ages showed wide variations

Discussion

This study shows that two forms of hypertensive vascular change can be recognized in the pulmonary vascular bed The arterial form is caused by conditions which elevate the pulmonary arterial pressure without affecting the venous pressure The venous type is produced by left sided congestive heart failure which has not only an elevation of the venous pressure but also elevation of pressure throughout the pulmonary circulation The pressure relationships across the pulmonary vascular bed for normal arterial HPVD and venous HPVD are shown diagrammatically in Fig 9

In arterial HPVD the major loss of pressure energy between the hypertensive arteries and normotensive veins probably occurs at the arterioles.[1] These vessels regulate flow by changing resistance through altering the degree of medial constriction Presumably when arterial pressure is abnormally elevated the excess energy of the flowing blood is dissipated by resistance of the constricted arterioles This would protect the capillary bed from exposure to high blood pressure Several morphologic observations suggest that endothelial cells with reduced shear on their lumenal surface are stimulated to enlarge and proliferate The early morphologic changes in the arterial intima in arterial HPVD resemble this change The mechanism by which shear forces would be decreased in this condition is obscure possibly local arteriolar boundary layer separation could develop Once initiated the

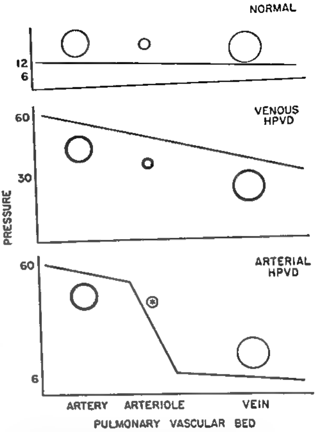

Fig 9 Diagram showing representative blood pressures across the pulmonary vascular bed in normal subjects venous HPVD and arterial HPVD Note that artery pressure is similar in both forms of HPVD but resistance at the arterioles leads to normal vein pressure in arterial HPVD

process could be perpetuated by the narrowing of the lumen produced by the intimal cell proliferation itself (see Fig 10) and a region of boundary layer separation at the downstream end of the lumenal narrowing produced by intimal cell increase would provide a setting for the marked proliferation which produced the glomoid

Enlargement of glomoids is probably abetted by small deposits of fibrin since these may be seen occasionally in these lesions The dilated postglomoid precapillary vessels which constitute the angiomatoid characteristic of advanced arterial HPVD lesions are probably best regarded as poststenotic dilatations The terminal stage of arterial HPVD is characterized by hypertensive necrosis of the arteries proximal to the stenosis produced by the arteriolar intimal proliferation and glomoid Necrosis was seen only after long standing and severe pulmonary hypertension

The morphologic changes found in the pulmo

Fig 5 Grade V1 with cellular intimal proliferation in the artery (top) and normal vein (bottom) (Both Verhoeff-van Gieson ×200)

Fig 6 Grade V2 with intimal fibroelastosis in the artery (top) and cellular proliferation in the intima of the vein (bottom) (Both Verhoeff-van Gieson ×200)

Fig 7 Grade V3 with severe intimal fibroelastosis in the artery (top) and IFE in the vein (bottom) (Both Verhoeff-van Gieson ×200) The insert shows the newly formed elastic fibers in the venous intima (Verhoeff-van Gieson ×1 000)

Fig 8 Grade V4 with healing hypertensive arteritis from a patient with congenital mitral stenosis (Verhoeff-van Gieson ×120)

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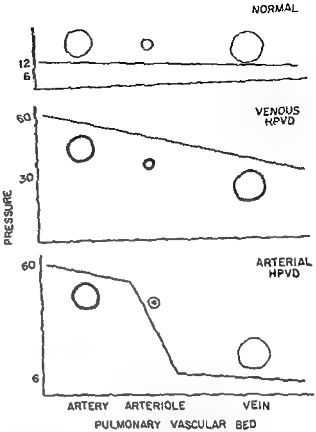

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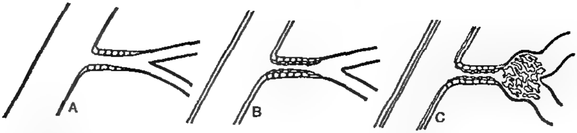

Fig 10 Diagram of the probable stages in development of arterial HPVD lesions In *A* there is constriction of the lumen by medial contraction leading to intimal cell proliferation in the constricted segment as shown in *B* The morphology resembles the change associated with reduced surface shear but the exact local hemodynamics are unknown In *C* the glomoid is shown formed distal to the region of constriction produced by intimal cell proliferation The glomoid develops from intimal cell growth into zones of boundary layer separation and into small foci of fibrin deposition The distal precapillary arterioles undergo poststenotic dilatation In late stages the parent trunk may undergo hypertensive necrosis

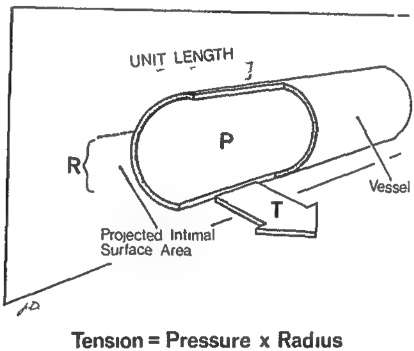

Fig 11 Diagram of the relationship between pressure and vessel size and the tension in the wall Increased tension correlates with development of intimal fibroelastosis in the arteries and veins in venous HPVD and in the arteries in arterial HPVD

nary vascular bed of patients dying with idiopathic pulmonary hypertension were the same as those seen in patients with a ventricular septal defect or patent ductus arteriosus The grade of arterial HPVD found in IPH correlated well with the severity of pulmonary hypertension measured clinically However, duration of the disease process could not be determined and the severity of lesions showed no correlation with age alone Since the morphologic changes in IPH are those of arterial HPVD, it seems probable that they develop secondary to constriction of the pulmonary arterioles with subsequent structural changes as proposed above In the absence of any evident explanation for elevated blood pressure in the main pulmonary arteries in these patients it may be that an inappropriate constriction of the arterioles is the primary abnormality in IPH

In venous HPVD the blood pressure is elevated throughout the entire vascular bed (see Fig 9) The effect of pressure increase in the blood vessel is to increase the mural tension as indicated diagrammatically in Fig 11 Several studies have shown that fibroelastosis is the response of the endocardium and intima to increase in tension[8] In the present study there is a correlation between the duration and severity of elevations of pulmonary blood pressure and the degree of development of intimal fibroelastosis It seems appropriate to consider IFE as an adaptive

response which *strengthens the vessel* wall to increased *tension* *It should be noted that IFE is* regularly seen in the pulmonary arteries but not in the veins in the cases with the arterial form of HPVD Unlike the changes which occur in the arterioles in arterial HPVD IFE does not appear to appreciably narrow the vascular lumen of either arteries or veins

Descriptions of the sequence of histologic changes found in arterial HPVD have been made *previously*[9] *As in the present study a correlation* was *found* between severity of intimal changes and the duration and severity of pulmonary hypertension in patients with ventricular septal defects or patent ductus arteriosus

Identification of the type of HPVD is of importance since the cause development and functional significance of the two forms differ Arterial HPVD lesions are associated with *primary elevation of pulmonary artery* pressure are characterized by *complex intimal cell prolifer*ations in artrioles and lead to *progressive struc*tural changes obstructing the lumen Venous HPVD lesions are associated with elevation of pressure throughout the pulmonary vascular bed are characterized by intimal fibroelastosis in both arteries and veins and structurally produce only a strengthening of the vascular wall The grading system *for HPVD lesions described* is based on easily recognized qualitative *changes in intimal* morphology The categories correlate with severity and duration of pulmonary hypertension

Summary

Autopsy observations suggested that lesions of hypertensive pulmonary vascular disease (HPVD) *due to elevated venous pressure* differ from those with arterial *hypertension only* Clinical and pathologic features were reviewed in patients from the Hopkins autopsy files with proved pulmonary hypertension 50 had venous HPVD due to left sided congestive heart failure 50 had *arterial* HPVD due to congenital malformations *and* 15 had idiopathic pulmonary hypertension (IPH)

The two forms of HPVD have *consistent* distinctive histologic changes In venous HPVD intimal fibroelastosis (IFE) develops in veins and arteries with retention of normal lumen diameters Intensity of IFE correlates with severity and duration of venous hypertension Arterial HPVD has IFE in conducting arteries but the characteristic lesion is cellular intimal proliferation in regulatory arterioles producing progressive irreversible lumenal narrowing Glomoid and angiomatoid lesions appear with prolonged severe arterial *hypertension* *They do not occur in venous HPVD* *Hypertensive arteritis may devel*op with either form of HPVD IPH has arterial type HPVD

IFE of venous HPVD appears to be a response to increased mural tension Arteriolar intimal cellular proliferations seen in arterial HPVD may be produced by blood flow boundary layer separations IPH may be explainable as protracted inappropriate pulmonary arteriolar constriction

REFERENCES

1. Burton A C *Physiology* and biophysics of the circulation Chicago 1965 Year Book Medical Publishers Inc.
2. Hutchins G M Coarctation of the aorta explained as a branch point of the ductus arteriosus, Am J Pathol. 63 203 1971
3. Hutchins C M and Maron, B J Development of endocardial valvuloids with valvular insufficiency Arch. Pathol 93 401 1972
4. Maron B J and Hutchins G M The development of the semilunar valves in the human heart Am J Pathol 74 331 1974
5. Salyer W R., and Hutchins G M Glomoid lesions in systemic arteries in malignant hypertension Arch Pathol 97 104 1974
6. Hutchins G M and Bannayan G A Development of endocardial fibroelastosis following myocardial infarction Arch. Pathol. 91 113 1971
7. Hutchins G [redacted] and Vie [redacted] A. The progression of interstitial myocarditis to idiopathic endocardial fibroelastosis Am J Pathol. 66 483 1972
8. Eagan J W Jr Salyer W R and Hutchins C M *The* pathogenesis of the renal vascular disease of progressive systemic sclerosis (abst) *Am J Pathol 74 19a* 1974
9. *Heath D* and Edwards J E The pathology of hypertensive pulmonary vascular disease A *description* of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects Circulation 18 533 1958
10. Heath D Helmholz [redacted] F Jr Burchell H B *DuShane J W* and Edwards, J [redacted] Graded pulmonary vascular changes and hemodynamic *findings* in cases of atrial and ventricular septal defect and patent ductus *arteriosus Circulation* 18 1155 1958

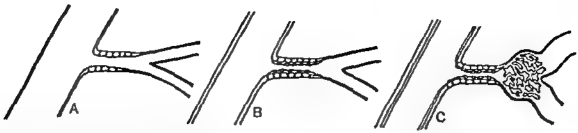

Fig 10 Diagram of the probable stages in development of arterial HPVD lesions *In A there is constriction of the lumen by medial contraction leading to intimal cell proliferation in the constricted segment as shown in B* The morphology resembles the change associated with reduced surface shear but the exact local hemodynamics are unknown In *C* the glomoid is shown *formed distal to the region* of constriction produced by intimal cell proliferation The glomoid develops from intimal cell growth into zones of boundary layer separation and into *small foci of fibrin deposition* The distal precapillary arterioles undergo poststenotic dilatation In late stages the parent trunk may undergo *hypertensive necrosis*

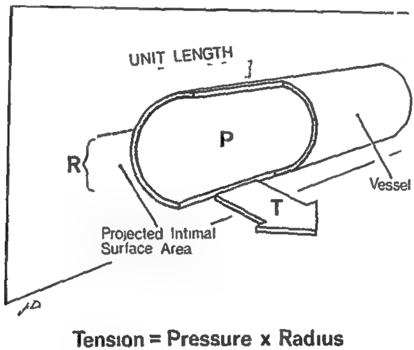

Fig 11 Diagram of the relationship between pressure and vessel size and the tension in the wall Increased tension correlates with development of intimal fibroelastosis in the arteries and veins in venous HPVD and in the arteries in arterial HPVD

nary vascular bed of patients dying with idiopathic pulmonary hypertension were the same as those seen in patients with a ventricular septal defect or patent ductus arteriosus The grade of arterial HPVD found in IPH correlated well with the severity of pulmonary hypertension measured clinically However duration of the disease process could not be determined and the severity of lesions showed no correlation with age alone Since the morphologic changes in IPH are those of arterial HPVD it seems probable that they develop secondary to constriction of the pulmonary arterioles with subsequent structural changes as proposed above In the absence of any evident explanation for elevated blood pressure in the main pulmonary arteries in these patients it may be that an inappropriate constriction of the arterioles is the primary abnormality in IPH

In venous HPVD the blood pressure is elevated throughout the entire vascular bed (see Fig 9) The effect of pressure increase in the blood vessel is to increase the mural tension as indicated diagrammatically in Fig 11 Several studies have shown that fibroelastosis is the response of the endocardium and intima to increase in tension[6,8] In the present study there is a correlation between the duration and severity of elevations of pulmonary blood pressure and the degree of development of intimal fibroelastosis It seems appropriate to consider IFE as an adaptive

hypertension a catecholamine secreting tumor must be excluded A short acting alpha blocker has been used to detect the circulating pressor agent This test gave many false positives so at the present time a better test is the detection of excessive vanilylmandelic acid (VMA) in the urine VMA is the ultimate metabolic product of a catecholamine in the human species During the surgical removal of a pheochromocytoma a short acting alpha blocker can be used to protect the patient against massive amounts of catechol amine released by manipulation of the tumor If a norepinephrine tumor is diagnosed a long acting alpha blocker can effectively control the intermittent episodes of hypertension

Some cases of peripheral vascular disease can be treated with an alpha blocking agent Neurogenic vasospasm seems to be associated with most types of peripheral vascular disease This spasm would be relieved by alpha blockade Unfortunately alpha blockade is not universally effective in improving peripheral circulation

A third use for alpha blockade is in the treatment of hypovolemic shock In this condition there is maximal vasoconstriction produced reflexly by the fall in arterial pressure as blood volume is lost In many vascular beds notably the renal and cutaneous blood flow essentially ceases In other vascular beds even though flow may continue tissue damage results Basically the alpha blockers relieve the vasoconstriction and allow blood flow to return Three things happen (1) with the increase in cardiac output blood flow returns or increases chiefly in the viscera (2) there is a local redistribution of flow that improves metabolite exchange and (3) there is a shift of fluids from interstitial spaces to the blood stream When alpha block is used in shock cardiac output must be continually monitored Volume should be restored by administration of blood plasma or substitutes The important point is some blood flow at any pressure is better than no blood flow at any pressure[1]

There are three alpha blocking agents in current use Phentolamine and tolazoline are imidazoline derivatives and short acting competitive blocking agents Their pharmacologic effect is complicated by their histamine like action Tolazoline is most complex in action In addition to alpha blocking and histamine like action it is also a beta agonist and muscarinic drug Fortunately all of its effects would be useful in peripheral vascular disease Phentolamine has been used to diagnose pheochromocytoma It is also used to treat accidental tissue infiltration by norepinephrine or dopamine It can be used to treat hypovolemic shock

Table I Adrenergic receptor blocking agents

A Alpha	
Competitive	
	Phentolamine (Regitine)
	Tolazoline (Priscoline)
Non competitive	
	Phenoxybenzamine (Dibenzyline)
B Beta	
Competitive	
	Propranolol (Inderal)

Phenoxybenzamine is classified as a nitrogen mustard In water it cyclizes into a reactive imine ring that acts as an alkylating agent This blocks the alpha receptor by changing it chemically This is a non competitive block Phenoxybenzamine has been used in peripheral vascular disease and in the treatment of pheochromocytoma It is used experimentally by intravenous administration to help treat hypovolemic shock

Beta blocking agents

No drug that would block the beta receptor was recognized until dichloroisoproterenol (DCI) was found to have this effect DCI is difficult to work with since it is a potent partial agonist the first dose always produces tachycardia and vasodilation At the suggestion of Black and Stephenson the beta blocker pronethalol was tested in angina pectoris Pronethalol was found also to be a partial agonist In addition it proved to be carcinogenic in mice Propranolol was then introduced as a substitute and was tested extensively in angina and hypertension [4] At about the same time other drug companies entered the field of beta blocker synthesis It has been ten years since propranolol was introduced into clinical medicine As yet it is still the only beta blocker approved by the Food and Drug Administration

What are the cardiovascular effects of beta blockade? These are confined mainly to the heart The first effect seen in a patient at rest is a removal of sympathetic control of the heart This results consistently in bradycardia However the negative inotropic effect may be unmeasurable

Appraisal and reappraisal of cardiac therapy
Edited by Arthur C DeGraff and Julian Frieden

Present state of alpha and beta adrenergic drugs
II The adrenergic blocking agents

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Adrenergic blocking agents are substances that have affinity for adrenergic receptors but do not have potency This means that the blocking drug makes a good fit with the receptor but this interaction does not result in an effector response However, now the receptor cannot respond to an agonist since the receptor is occupied by the blocking molecule

Blocking agents have also been called adreno lytic agents This term can also include agents that can interfere with the biosynthesis storage, or release of the transmitter The difference between these drug classes is of clinical impor tance Adrenolytic agents can produce a total chemical sympathectomy The blocking agents produce selective chemical sympathectomy

There are specific blocking agents for alpha receptors and specific blocking agents for beta receptors It is not usual to find an agent that blocks both receptors, no drug of this type is in clinical use The blocking agents used in clinical practice at the present time are listed in Table I

Alpha blocking agents

Drugs of this type have been known for many years Ergot alkaloids were used in the laboratory to produce the pharmacologic phenomenon called epinephrine reversal The original reversal experi ment was done on rabbit uterus Epinephrine normally causes this organ to contract After alpha blockade with ergotoxine epinephrine caused the uterus to relax The standard epineph rine reversal test is on the arterial pressure of an anesthetized animal Epinephrine normally pro duces a pressor response Following alpha block ade a depressor response is produced Although the mechanism of this response was at the time puzzling we now know it to be due to unmasking of beta receptor responses

The discovery of a good alpha blocking agent, dibenamine by Nickerson and colleagues in 1947 served as a stimulus for investigation of the alpha receptor This also stimulated the search for new and better alpha blocking agents

What are the cardiovascular responses to an alpha receptor blocking agent? If there is no ongoing adrenergic activity no response will be seen For example in a patient in the supine position administration of an alpha block will not significantly change heart rate or blood pressure As soon as the patient stands hypotension and tachycardia will appear Under the influence of gravity the blood moves footward The drop in pressure in the carotid sinus triggers the afferent limb of the vasoconstrictor reflex through the vasomotor center This normally prevents the accumulation of blood in the lower extremities With the alpha receptors of the peripheral arteries arterioles venules and veins blocked the vasoconstriction cannot occur Thus the pressure in the head falls acutely and fainting results

The efferent side of this reflex to the heart is unaffected Through beta receptors sympathetic stimulation of the heart occurs The severe tachy cardia and the palpitations make it impossible to use alpha blockers in essential hypertension

The alpha blocking agents have three general cardiovascular uses These are (1) diagnosis and treatment of pheochromocytoma and related disorders (2) treatment of vasospastic peripheral vascular disease and (3) treatment of hypoval emic shock

In pheochromocytoma or neuroblastoma there is an excess of circulating epinephrine norepi nephrine or both In the differential diagnosis of

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curve and effect on electrocardiogram at rest and on exercise, Br Heart J **33** 4 3 1971
6. Black, J W Duncan W A and Shanks R G Comparison of some of the properties of pronethalol and propranolol, Br J Pharmacol **25** 577 1965
7 Prichard B N C and Gillam P M S Use of propranolol (Inderal) in treatment of hypertension Br Med J **2** 25 1964
8. Prichard B N C and Gillam, P M S Treatment of hypertension with propranolol Br Med J **1** 7 1969
9 Wit A L Hoffman B F and Rosen M R Electrophysiology and pharmacology of cardiac arrhythmias IX Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade Part B AM HEART J **90** 665 1975
10 Lands, A M Arnold A McAnliff J P et al Differentiation of receptor systems activated by sympathomimetic amines Nature **214** 597 1967

The heart, even at rest, is always under some adrenergic control. Therefore, to acertain the presence of beta block a special test must be applied. The more sensitive method is a block of isoproterenol induced tachycardia. A more physiologic method is the block of exercise induced tachycardia. It is easier to block exogenous catecholamine, but the clinical objective is to block the transmitter released from an adrenergic nerve end.

As the dose is increased, there appears a measurable slowing of A V conduction. Large doses can produce complete heart block.

In the failing heart the actions of beta blockade become more apparent. All fast arrhythmias seem to have a sympathetic component. Therefore, beta blockade will in all cases slow the ventricular rate. This effect would improve cardiac output. Increased sympathetic activity is one of the compensatory mechanisms in congestive failure. Beta blockade by removing cardiac sympathetic support could evoke acute failure. Beta blockers should not be given to patients with untreated congestive failure. Digitalis should always be given prior to propranolol.

There is another condition under which the negative chronotropic and inotropic effects of beta blockade become very apparent. Certain anesthetics, such as ethyl ether, activate the sympathetic system. Heart rate is fast, the myocardium is stimulated, and cardiac output is increased. Now a beta blocker would slow the heart, weaken the myocardium, and produce an acute fall in cardiac output and blood pressure by removal of the sympathetic action.

Adrenergic vasodilation is blocked by beta blocking agents. All blood vessels have both alpha (constriction) and beta (dilation) receptors. The balance between alpha and beta varies from vascular bed to vascular bed. Cutaneous and renal beds seem to have only alpha receptors, beta agonists or blocking agents have no significant action here. Nutrient vessels in skeletal muscle seem to have mainly beta receptors; this is the site of depressor action of epinephrine or isoproterenol. Coronary vessels have both receptors. However, coronary flow is controlled by metabolites rather than by nerves.

The general vascular effect of a beta blocker would be a slight increase in peripheral resistance. In most cases this would be insignificant. If however there is impaired circulation a beta blocker might worsen the condition.

Two beta receptors?

On the basis of a comparative study of beta agonists, Lands and associates[16] proposed the existence of at least two different receptors. Beta 1 was associated with the heart, and beta 2 with smooth muscle in bronchi and blood vessels. This idea has gained wide acceptance and beta drugs are often classified according to which receptor they mainly act on. Although useful as a classification concept, this idea is probably not complete.

A simpler explanation of this receptor selectivity is based on a variable structure-activity ratio for each receptor. As will be described further in the next paper in this series, this variable receptor selectivity may have more laboratory interest than clinical application.

Summary

There are selective blocking agents (antagonists) for alpha receptors and beta receptors. These blocking agents prevent the response to injected agonists and neurogenically released norepinephrine.

The principal cardiovascular response to alpha blockade is postural hypotension with reflexly induced cardiac stimulation. If neurogenic vasoconstriction is present, this will be removed.

The principal cardiovascular response to beta blockade is bradycardia. If fast arrhythmias are present, these will be slowed. Beta blockade tends to increase peripheral resistance. Unless circulation is previously impaired this vasoconstrictive effect is insignificant.

REFERENCES

1. Slater I H, and Powell C E: Blocking of inhibitory adrenergic receptors by a dichloro analogue of isoproterenol. J Pharmacol Exp Ther 122:480, 1958.
2. Moran N C, and Perkins M E: Adrenergic block of the mammalian heart by a dichloro analogue of isoproterenol. J Pharmacol Exp Ther 124:223, 1958.
3. Black J W, and Stephenson J S: Pharmacology of a new adrenergic beta receptor blocking compound (nethalide). Lancet 2:311, 1962.
4. Gillam P M S, and Prichard B N C: Propranolol in the therapy of angina pectoris. Am J Cardiol 18:366, 1966.
5. Prichard B N C, and Gillam P M S: Assessment of propranolol in angina pectoris. Clinical dose response

D B Steed, G R Thorne M G Jones S Guerrier C J Eraut, C D McHugh I M Chowdhury N R Jafary M H and Wallace T J Acute myocardial infarction Home and hospital treatment Br Med J 3 334, 19 1
3. Hampton J R Morris G K and Mason C Survey of general practitioners attitudes to management of patients with heart attacks, Br Med. J 4 146 1975
4 Hayes, M J Morris, G K., and Hampton J R. Comparison of mobilisation after two and nine days in uncomplicated myocardial infarction Br Med J 3 10 1974

DI the conduction system and myocardial function

Physicians, as well as physiologists fail to realize that the time course of contraction of all portions of the myocardium is extremely important for efficient and effective emptying of the ventricle For example, if the outflow tract of the right or left ventricle were to contract first in the cardiac cycle the outlet of the ventricles would be sphincterally partially closed to some degree thus impairing outflow and emptying of blood But, this does not occur in normal hearts because the electric impulse which initiates ventricular contraction is delivered to the septal and apical regions of the heart first and to the bases last The order of activation of the myocardium depends upon the anatomic distribution and function of the conduction tissue of the heart Thus, the order of ventricular myocardial *contraction is predetermined by the order of* ventricular myocardial depolarization or electric activation The order of electric activation is genetically and developmentally determined *in utero* When this is entirely normal, ventricular myocardial pumping function is *normal and orderly* in its time course We have found two normal patterns of order of time course of ventricular activation or depolarization displayed in the spatial vectorcardiogram

When the order of electric activation or time course of depolarization of the myocardium is disordered, ventricular contraction becomes disordered and, in turn myocardial function is disturbed The ventricle becomes less efficient and less effective which can lead to clinically recognizable diseased cardiac states. For example with RBBB and LBBB the order of ventricular myocardial contraction is definitely abnormal. It is even more abnormal or more disordered when disease of the Purkinje network or arborization block or defective intraventricular *conduction (defective IVC)* is present The order is abnormal when artificial pacemakers are driving the heart Such disturbance in the order of ventricular depolarization could conceivably occur on a congenital basis *with* abnormal anatomic distribution or function of the Purkinje network or because of anatomic or morphologic disease and/or on a purely functional basis, or in therapy as with the use of a pacemaker This would lead to dysfunction of the myocardial and systolic ventricular contraction and ejection *In fact, such a mechanism could readily explain the* development of subaortic or subpulmonic (crista supraventricularis hypertrophy) hypertrophic obstruction If these outflow tract areas were depolarized early in the cardiac cycle work" hypertrophy would occur initially and myocardial degeneration or disease would develop later Such disordered activation could produce the hemodynamic manifestations described for ventricular outflow obstruction due to hypertrophic subaortic stenosis or crista supraventricularis hypertrophy

One can readily imagine the multitude of myocardial dysfunctional states that could follow different disturbances in the order of electric activation of the myocardium regardless of the conceivable causes i e genetic developmental, morphologic therapeutic, and/or functional. It is impressive how orderly the time course of electric activation is in people all predetermined by development morphology and function

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REFERENCE

1 Burch G E., Abildskov J A. and Cronvich, J A. Studies of the spatial vectorcardiogram in normal man Circulation 7 558 1953

Epimembranous nephropathy

It is usually easy for the physician to diagnose the nephrotic syndrome massive proteinuria, hypoalbuminemia edema, and frequently though not always hypercholesterolemia form a complex that in most cases can hardly be overlooked hypertension may or may not be present Much more difficult however is the important *problem of the* subspecies of nephrosis the doctor is dealing with. Certainly the "minimal lesion or lipoid variety is most commonly seen in children the

Annotations

Coronary care at home?

There is still doubt at least in England whether a patient with a heart attack is best cared for at home by his family doctor or in hospital in a specialized unit Faced with a patient with chest pain the family doctor has to decide whether the stress of an ambulance journey and an admission to hospital will itself induce complications that would not occur if the patient s pain were relieved and he was kept in his own bed

A family doctor opting for home treatment has certain theoretical considerations to support him The most important is that half the deaths that are going to occur happen within two hours of the onset of symptoms and several studies have shown that the average patient has had symptoms for longer than this before calling for help There is a marked difference frequently not appreciated by cardiologists between patients who have their attacks at home and those whose attacks occur away from home in particular the former group tend to have had their symptoms for much longer than the latter In Nottingham England about three quarters of all heart attacks occur in patients at home and the family doctor sees them when the main risk period is over Patients away from home when their symptoms begin pose an entirely different problem for they are usually admitted to hospital by an ambulance that has been called by a member of the public so that the possibility of home care does not arise this is the group of patients who are admitted to hospital well within two hours of the onset of symptoms

The family doctor opting for home treatment also has on his side the only randomized study of home or hospital care for patients with heart attacks Although this study was open to certain criticisms—in particular only about a quarter of the patients with heart attacks were randomly selected for home or hospital care—the lowest mortality rate was found in the group where chance dictated that the patient should stay at home

As a preliminary to a further but differently organized study of home and hospital care of patients with heart attacks the family doctors in Nottingham were surveyed to determine their present preferences The survey took the form of a questionnaire based on three hypothetical patients whose case histories were provided

The first hypothetical case was a middle aged man in good social circumstances who was seen soon after the onset of classical symptoms of a heart attack and who had no problems other than pain The family doctors were asked whether they would care for him at home or admit him to the local Coronary Care Unit Over all 61 per cent of the respondents selected hospital care and 39 per cent home care there was a significant difference between those who qualified before 1960 and their younger colleagues who trained in the Coronary Care era in that more of the latter chose hospital admission

The second hypothetical patient was described in such a way that it was clear that his heart attack was accompanied by features suggesting a low cardiac output to see whether many family doctors consider such patients too ill to move Although it is probably in this group that hospitals have the least to offer and the hazards of transport are probably the greatest 70 per cent of family doctors said that they would arrange immediate hospital admission and 22 per cent said they would have the patient admitted after a few hours of home management Over all only 8 per cent of family doctors, mainly in rural areas said they would keep such a patient at home

A third hypothetical patient who was described as having an uncomplicated heart attack was said to refuse hospital admission and the family doctors were questioned about his management Seventy per cent said they would keep him in bed for less than a week although their opinions as to the best time of mobilization ranged from immediately after the pain had settled to four weeks The younger doctors indicated a preference for shorter durations of bed rest than their seniors but over all it was clear that family doctors followed much the same programme as their hospital based counterparts who mainly accept that 48 hours in bed is quite long enough for patients without complications

Obviously it is not possible to be certain that a family doctor will treat his real patients in the same way as he treated the hypothetical ones in the survey but the alternative way of establishing what is happening in the community which is to persuade family doctors to notify some coordinating center of any patient with a suspected heart attack which they treat is open to the equally valid criticism that the requirement of notification would probably alter the doctor s behavior A simple and perhaps not easily quantified conclusion from the Nottingham survey is that at least in this area a fairly large number of patients with heart attacks are cared for at home This very fact suggests that many family doctors are unconvinced of the value of hospital treatment for these patients and given the theoretical background and the only *clinical trial* so far published their belief cannot be criticized

A randomized study of home or hospital care for patients with heart attacks involving a two hour period of Coronary Care within the home has been in progress for the past two years, and a proper judgement of the value of Coronary Care at Home must await its completion

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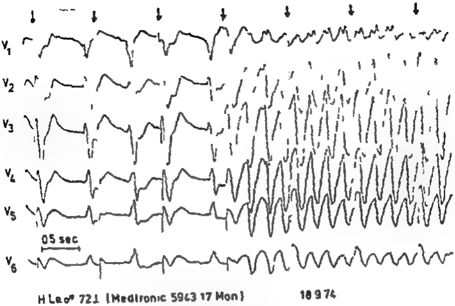
REFERENCES

1 Fulton M Julian D G and Oliver M F Sudden death and myocardial infarction Circulation 39(Suppl 4) 182 1969
2 Mather H G Pearson N G Read K L Q Shaw



Fg 1 ECG (Lead V to V) recording during pacemaker induced ventricular flutter The demand pacemaker is switched over to a fixed rate pacing mode The pacemaker stimuli (*arrows*) collide with the spontaneous idioventricular rhythm of the patient The fourth pacemaker impulse shows an R-on T phenomenon and ventricular flutter is induced

bipolar electrodes in humans and animals with pacemaker induced ventricular arrhythmias suggest that in the majority of instances an anode on or within the heart, of size and configuration to permit anodal stimulation is necessary to produce ventricular tachycardia or ventricular fibrillation in humans with permanent or temporary pacing systems

Meanwhile, we have observed ventricular fibrillation induced by cathodal stimulation in a patient without an acute myocardial infarction. In a 72 year old man with intermittent complete A V block a unipolar pacemaker (Medtronic 5943) had been implanted 17 months before The patient attended the pacemaker clinic because he had observed a pulse rate higher than normal during the pulse control in the morning The ECG showed an accelerated idioventricular rhythm as far as the few beats recorded before the onset of fibrillation allow this diagnosis Because of the relatively high spontaneous rate the pacemaker was inhibited In order to check up the demand pacemaker he was switched over to a fixed rate pacing mode by a magnet One of the first pacemaker stimuli which collided with the idioventricular beats showed the R on-T phenomenon and ventricular flutter was induced (Fig 1) After defibrillation by a precordial thump the patient was monitored for 48 hours in the CCU The ECG showed a sinus rhythm without any sign of myocardial infarction The serum enzymes (GOT CPK LDH) were in the normal range during this period We were not able to detect any abnormality in the arterial blood Po the acid base status or serum electrolytes The plasma digoxin level was 1 2 ng /L.

We conclude Unipolar cathodal stimulation is able to induce ventricular fibrillation if the stimulus collides with idioventricular beats. This can occur even in patients with implanted pacemakers without acute illness. Therefore no fixed rate pacemaker should be implanted even in patients with complete A V block The control of demand pacemaker function by magnet induced fixed rate pacing mode implies a possible hazard This is especially dangerous if the patient is testing the pacemaker at home and no defibrillator is available

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1 Preston T A Anodal stimulation as a cause of pacemaker induced ventricular fibrillation AM HEART J 86 366 1973

mesangiocapillary form is most common in adolescence and epimembranous nephropathy (EN) is most common in adults[1] But exceptions to these rules are so frequent that one is easily led astray by them In fact epimembranous nephropathy happens in all age groups Furthermore it is of more than academic interest to establish a precise histologic diagnosis for the prognosis and treatment are rather different for these varieties[2]

Nothing short of a renal biopsy can establish with certainty the precise diagnosis in such cases The tissue obtained by biopsy will show when submitted to special stains the underlying pathology[3] namely the presence of granular deposits of immunoglobulin G (IgG) and complement on the epithelial surface of the glomerular basement surface these deposits tend to be separated by spikes emanating from the basement membrane at a later stage they are englobed in what appears to be a thickened basement membrane Hence the correct term for the disease is epimembranous nephropathy albeit because this term is easier to distinguish from membranoproliferative nephropathy Electronmicroscopy and immunofluorescence study of the tissue brings out all these features in greater detail

The etiology of EN is obscure Indeed in the vast majority of cases no cause can be found however in many patients such a cause can be determined heavy metal intoxications some viral diseases (especially hepatitis virus B) administration of some drugs e g Tridion gold penicillamin etc Thus ironically some drugs that can cause EN are the ones used to combat the very maladies that in themselves may cause EN rheumatoid arthritis syphilis malaria etc Thus as the reader sees the causes of EN are multiple diabetes sarcoidosis lupus and other collagen diseases also join the ranks of occasional culprits Much more ominous is the bizarre asso ciation of EN with lymphomas carcinomas etc What s more the nephrotic syndrome can appear in a patient with well established malignancy concomitantly with the inchoate stage of malignancy or in some cases antecede it by weeks or even months Hence the wise physician should not be satisfied with the diagnosis of EN but is bound to search carefully for possible underlying or evolving lymphoma etc Fortunately the removal of a cause when this is known frequently leads to the removal or at least remission of the renal complication

Yet such remissions occasionally happen in cryptogenetic cases also and even without treatment this makes it quite difficult to gauge the prognosis in any individual person Nonetheless it is generally accepted that EN is a serious disorder usually leading to renal failure and death after several years of duration Hence the importance of treatment The general measures of low salt diet abundant protein intake and diuretics suffice in many patients at least to alleviate the condition In a significant proportion of patients, however this therapeutic armamentarium is insufficient Most nephrologists are very skeptical about the value of corticosteroids some however do find them quite efficacious[4] Evermore contentious is the role of cyclophosphamide we are convinced of its usefulness as an adjuvant of steroids On the other hand dipyridamole is still sub judice The latest arrival into the field of therapeutic agents is indomethacine Its definite role will be awaited with impatience by those physicians who care for patients afflicted with EN

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REFERENCES

1. Salomon M I Hsu K and Tchertkoff V Membranous nephropathy An overview J Am Geriatr Soc 23 535 1975
2. Pollak V E Pirani C L and Clyne D H The natural history of membranous glomerulopathy in Kincaid Smith P Mathew T and Becker E L editors Glomerulonephritis New York 1973 John Wiley & Sons Inc Publishers p 423
3. Heptinstall R H Pathology of membranous glomerulonephritis in Kincaid Smith P Mathew T and Becker E L editors Glomerulonephritis New York 1973 John Wiley & Sons Inc Publishers p 415
4. Lewis M H Loughridge L W and Phillips T M Immunologic studies in nephrotic syndrome associated with extrarenal malignant disease Lancet II 134 1971
5. Simon N M Indomethacin treatment of refractory nephrotic syndrome Kidney Int 8 420 1975

Ventricular fibrillation induced by a unipolar implanted pacemaker (cathodal stimulation)

In 1973 Preston stated in this journal A search of the literature showed that every documented episode of pace maker induced ventricular tachycardia/fibrillation in humans has been with a bipolar electrode system The association of

bet een the epidemiology of the two diseases as well Thus mortality rates from both cardiovascular and cerebrovascular disease are lower in hard water than in soft water areas so the path genesis of the two diseases mu t be similar in some important a pects besides being different in others. It is this aspect of the problem which seems consistent with two distinct–but related–faults of cholesterol metabolism

I do not know why precipitation ■ restricted to cerebral arteries. A conjecture I can offer is that precipitation might be a two-step process In the first instance some pathogen may modify blood cholesterol without any effect on its tran porta bility Precipitation then may occur when an attempt is made to withdraw it from the circulation in the organs where cholesterol is normally utilized namely the brain and the adrenal. Atheromatous plaques are found in both organs even if atheroma of the adrenal has little clinical significance

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REFERENCE

1 Statistisches Jahrbuch der Deutschen Demokratischen Republik, 1974

Ventricular performance during ejection

To the Editor

We wish to comment on the article by Stein and Sabbah entitled Ventricular performance measured during ejection Studies in patients of the rate of change of ventricular power (AM HEART J 91 99 606 19 6)

Theoretical and practical advantages of peak power derivative o ■ peak flow acceleration as ejection phase contractility indices are not impressive Both have fluid dynamic basis and physiological meaning. The power index ■ associated with energy concepts while the flow index is associated with momentum Momentum and energy equations are both needed to describe fluid dynamic systems

The authors earlier report as well as the present reference indicate high correlation between peak power derivative and peak flow acceleration These data from patients plotted in Fig. 1 show a relationship equally as good as that found for the dogs by Stein and Sabbah The lower peak flow accelerations in the dogs in control state and during propranolol are compatible with well known negative inotropic effects of anesthesia

High correlation between peak power derivative and peak blood acceleration in ejection phase is a consequence of low values of pressure derivative in this period of the cardiac cycle That is, the first term on the right hand side of Equation (1) in Stein and Sabbah is dominated by the second The first term typically accounts for only 1 to 5 per cent of the power derivative. The second which contains the flow derivative contributes the other 95 to 99 per cent For practical purposes, then, maximum power derivative is nearly a simple linear function of maximum flow derivative The negative regression intercepts on power axis and linear dispersals of experimental points in the authors data clearly support this observation

It is conceivable that there may be hemodynamic situations in which maximum power derivative has important indepen

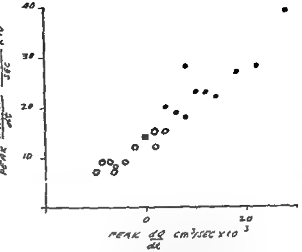

Fig 1 Ventricular performance of patients with normal (black circles) and abnormal (clear circles) ventricular function plotted from Tables I and II (pp 601 and 603) of Stein and Sabbah

dent information not possessed by peak flow acceleration We feel that this possibility alone provides reason enough for further investigation However maximum power derivative is a complex index which demand exceptional skill in catheterization and extraordinary prowess in data analysis methodologies. For users without these resources there are no practical disadvantages in use of maximum flow acceleration as the ejection phase contractility index

Maximum flow acceleration has further attractiveness in that it can be estimated quite well even without catheterization Theoretical and experimental studies ■ ing ultrasound and ballistocardiography strongly support the relationship of these noninvasive techniques to peak flow derivative It is unfortunate that their applicability is not more widely appreciated Catheterization is justifiable in only a small fraction of cases in which such objective information on heart function can make a positive contribution to research in human beings or characterization of patients.

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REFERENCES

1 Stein P D and Sabbah H N Rate of change of ventricular power An indicator of ventricular performance during ejection AM HEART J 91 219 19 6
2 Prandtl, L. and Tietjens O G Fundamentals of Hydro- and Aeromechanics Dover 195"
3 Malt R. A Depressant effect of ether on the heart AM HEART J 55 5 2, 1958.
4 Gams, E Chimoskey J E., and Huntsman L. L. Transcutaneous blood flow measurements in the aorta

Letters to the Editor

Serum glycoproteins in acute myocardial infarction

To the Editor

We have read with great interest the excellent paper of Snyder and co workers (AM HEART J 91 582 1975) In this paper they published the results of the lipid and glycoprotein investigations delivered in acute myocardial infarction The study of the individual serum glycoproteins having specific chemical structure and immunological properties is very important in acute myocardial infarction too because these investigations could result in data of pathogenetic and diagnostic value

We have estimated the changes in serum concentrations of glycoproteins in patients with acute myocardial infarction over 40 days after the acute attacks The observation time was divided into seven periods

The elevation in serum concentration of IgG reached its highest value on days 15 to 21 and on days 33 to 40 it was at the normal value The IgA concentration was significantly elevated on days 15 to 21 The serum concentration of IgM decreased on days 1 to 3 but did not deviate from the normal value after that The elevation of the ceruloplasmin level was significant on days 1 to 3 reached its maximum on days 3 to 7 and decreasing it remained higher on days 27 to 33 too The increase in the concentration of the α_2 macroglobulin was significant only on days 3 to 7 The decrease of the transferrin level was observable as early as on days 1 to 3 reached its minimal levels on days 15 to 21 and later on it came more and more to the normal value More detailed data have been published

Our results are not in full concordance with those of Snyder and his co workers regarding IgM and transferrin The decrease in concentration of transferrin merits special interest because it is in a good relation with the known negative acute phase reactant character of this glycoprotein Our observations made during a longer period of the illness have given further data to the dynamic of the alterations

We think it is useful to publish all results even though they are not in full concordance with each other because this will force us to solve the contradictions in order to acquire more exact information

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REFERENCE

1 Jakab L Feher J Siró I Szondy E and Szekely J Serum glycoproteins in myocardial infarction Acta Med Acad Sci Hung 31 69 1974

Faults of cholesterol metabolism

To the Editor

In the Editorial in the March issue of JOURNAL I was interested to read the hypothesis that cardiovascular disease is caused by a fault of cholesterol metabolism which imparts to particles of cholesterol an abnormally strong tendency to stay in suspension in water and makes their withdrawal from the plasma difficult It seems true that in hypercholesterolemia particles of cholesterol for an unknown reason circulate uselessly in the bloodstream and their removal by lipophages makes some kind of fault reasonable to suspect The hypothesis therefore is in accordance with observed facts and has a good explanatory value

The same does not apply to the second part of the hypothesis There seems little evidence in favor of the assumption that cerebrovascular disease is caused by uncontrolled precipitation of lipoproteins But even if it is assumed that some chemical combines with them and causes them to precipitate this would presumably occur in any part of the circulatory system where the two reactants come in contact with each other not necessarily only in cerebral arteries

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REFERENCE

1 Seely S Possible reasons for the comparatively high resistance of women to heart disease AM HEART J 91 275 1976

Reply

To the Editor

Efforts of formulating hypotheses of atherogenesis are still only at the stage of groping I certainly cannot claim that my hypothesis arranges all the jigsaw pieces in the correct formation

The main reason why it is necessary to stipulate two faults of cholesterol metabolism not one is that the epidemiologic distributions of cardiovascular and of cerebrovascular disease are as different as if they were two entirely independent diseases In the United States for instance the mortality rate from cardiovascular disease is three times as high as from cerebrovascular disease in Japan or Portugal the ratio is the reverse Or for example the mortality rate from cerebrovascular disease in East Germany has approximately halved between 1967 (when the crude mortality rate was 175 per 100 000) and 1972 (when the rate was 90 per 100 000) without any corresponding change in mortality rates from cardiovascular disease If there were only some marginal differences in the pathogenesis of the two diseases mortality rates from one could not change significantly without some changes in the other

On the other hand there are some obvious similarities

geous. Invasive studies, however such as those we reported are necessary to evaluate various approaches.

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REFERENCES

1. Stein, P D and Sabbah H N Rate of change of ventricular power An indicator of ventricular performance during ejection AM HEART J 91 219 19 6
2. Stein P D and Sabbah H N Ventricular performance measured during ejection Studies in patients of the rate of change of ventricular power AM HEART J 91 599 1976
3. Stein P D and Sabbah H N Force velocity length relations in man expressed by a single hemodynamic expression The ejection rate of change of power at peak tension, Am J Cardiol. 37 8/1 1976
4. Stein, P D McBride G G and Sabbah H N Ventricular performance and energy of compression power and rate of change of power during isovolumic contraction Cardio asc. Res. 9 29 1975
5. Stein P D and Sabbah H N Ventricular performance in patients based upon the rate of change of power during isovolumic contraction Am J Cardiol 35 258 1975
6. Stein P D and Blick, E F Arterial tonometry for the atraumatic measurement of arterial blood pressure J Appl. Physiol. 30 593 1971
7. Sabbah, H N and Stein P D Arterial cuff tonometry A semi invasive method for the instantaneous and phasic measurement of blood pressure Med. Instrum 10 189 19 6

What does the doctor really mean when he says Hmmm ?

To the Editor

Perhaps the most frustrating realization for the computer designer or programmer when working with physicians is that the physician cannot *express in quantitative terms precisely* what it is that he looks for listens for or observes that tells him whether his patient is doing well or poorly whether or not he has a particular disease and whether he needs a particular kind of medical attention So long as this is the case of course the computer is relegated to the job of storing retrieving and sorting data making comparisons, and performing statistical analysis, all of which it *does very well and very quickly* But the capabilities of the computer remain largely untapped if it is restricted to such activities.

In our own laboratory we have had occasion to perform computer analysis of the vascular sounds associated with arterial stenosis, and we discovered that it was possible to extract a *very faint* murmur from a rather loud background of normal heart sounds by *a process which now appears to* resemble what the physician's ear brain computer actually does *unconsciously* But in that case it turns out that the computer actually does it better It is suggested here that this process (described below) is generally applicable in medical problems and can in fact be programmed for a wide variety of applications.

In the case of sounds if one takes a repetitive signal such as the heart sounds, with a superimposed repetitive broad band sound such as a murmur and averages it over a number of heart beats then the broad band murmur sound is cancelled out being nonsynchronous thus leaving just the background heart sound which is synchronous. If the resulting signal is then squared we have the power of the heart sound alone i e without the murmur But if the process is reversed squaring first and then averaging then we have the sound power of the entire signal including the murmur Thus the difference between these two processed signals gives the actual sound power of the murmur with the heart sounds removed In this manner without filtering out any signal information we can extract that portion of the signal which is "abnormal" But as it turns out this process is the mathematical equivalent of extracting what is known as the "variance" of any quantity from some background norm It is in fact this precise mathematical definition which then allows the use of the computer to carry out this process. The mathematical expression of this process is

$$p(t) = \frac{1}{N}\left\{\sum_{1}^{N} x_n^2 \ (t) - \frac{1}{N}\left[\sum_{1}^{N} x\ (t)\right]^2\right\}$$

where x (t) is the sound amplitude at time t in the nth heartbeat and p(t) is the sound power of the murmur alone

In another application we have been involved with the problem of defining the degree of aggregation of red cells as seen under the microscope Here again it becomes evident that our eyes quickly pick up an over all impression in which the *distinguishing feature of an abnormal sample is the variance* in light intensity as we scan across the field of view Thus, a normal unaggregated sample will show a very uniform field of essentially single cells and short rouleaux never more than a single cell in thickness. Pathologic samples, on the other hand show themselves as more discrete three dimensional collections of cells tightly bound together with consequent large reductions in light transmission in those locations, leading to an increased variance in light intensity

In view of these observations, it is suggested that a first attempt at computer diagnosis might be based on a calculation of the variance in whatever parameter is being recorded thereby using the *patient as his own control*

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REFERENCE

1. Tickner E G Boyers, D and Sacks A H *A method for detecting and quantifying faint cardiovascular murmurs,* Angiology Vol 2 No 7 July August, 19 6

with use of ultrasonic doppler instruments Verh Deutsch Ges Kreislaufforsch 40 144 1974
5 Baan J Machester J H and Shelburne J C A quantitative relationship between the H I slope of the head food Bcg and the initial acceleration of flow in man Bibl Cardiol **29** 55 1972

Reply

To the Editor

In response to the letter of Drs Harrison and Smith we believe that insight relative to hemodynamic parameters as they relate to ventricular performance is derived from consideration of the rate of change of power During the ejection phase of contraction the rate of change of power showed an interrelation of pressure flow rate of change of pressure and rate of change of flow which without knowledge of this equation would stand as diverse and unrelated empirical indices [2] Further inspection of the equation as shown in Appendix 1 [1] permits one to consider the rate of change of power in terms of tension length and rate of fiber shortening A wide variety of previously derived empirical indices therefore are included in this equation To some extent their relation to each other and their relation to cardiac function can be interpreted in regard to how they relate to the rate of change of power In this sense we believe the rate of change of power to be an integrative expression which consolidates numerous previously derived empirical indices of performance

If one investigates the ejection rate of power further and measures it at peak ventricular wall tension then one obtains an expression which shows force velocity and length as a simple and interrelated set of parameters [3] Even contractile element velocity can be incorporated among the diverse indices encompassed in the ejection rate of change of power when measured at peak tension

During the isovolumic phase of contraction by consideration of the rate of change of power expressed in a different form we were able to derive a meaningful functional index of performance that circumvented assumptions implicit in other isovolumic indicies

From a physiological point of view therefore we believe that there is information in the expression for the rate of change of power and implications related to the interpretation of cardiac function that cannot be derived from a variety of empirical indices including the rate of change of flow The rate of change of power is of interest conceptually as a basis for further understanding of cardiac performance

Regarding fluid dynamic considerations of a theoretical nature when dealing with isothermal systems it is not necessary to utilize both the momentum and the energy equations for description of the system If isothermal conditions are being considered one can derive the momentum equation from the energy equation (To the first approximation the heart can be considered as an isothermal system) Energy is usually a more convenient form to use in describing fluid dynamic systems than momentum since energy is conserved

Although the maximal ejection rate of change of power was linearly related to the maximal rate of change of flow there was some scatter The term which includes the rate of change of flow accounts for an average of 89 per cent of the maximal rate of change of power Therefore the other term contributes an average of 11 per cent (range 5 to 17 per cent) in contradistinction to the amount cited by Drs. Harrison and Smith Since the maximal rate of change of power does not occur at the same instant as maximal rate of change of flow one cannot calculate the per cent contribution of each term from maximal values of pressure flow and their derivatives This may explain the difference in their estimates of the contribution of the second term and the actual contribution of the second term The maximal rate of change of power showed no overlap of values between normal and abnormal patients The rate of change of flow showed overlap of one patient and this is also shown on the graph submitted by Drs. Harrison and Smith In view of their comments probabilities were computed to determine the likelihood that an abnormal subject would be closer to the mean of the normal population than to the mean of the abnormal population This was accomplished by assuming that both of the indices are normally distributed and using the sample estimate for means and standard deviations The ejection rate of change of power measured in abnormal subjects appeared to be less likely to show a normal value ($P = 0.02$) than a rate of change of flow ($P = 0.05$) More striking results were shown when the ejection rate of change of power was measured at peak tension In that case the likelihood that an abnormal subject would show a value closer to the mean of the normal population than the abnormal population was $P = 0.0000002$ Thus minor differences of ability to distinguish between normal and abnormal performance appear to be shown between the maximal ejection rate of change of power and the maximal rate of change of flow This may suggest a preference for the former index At peak tension the ejection rate of change of power showed sharp differences which indicate a practical advantage of it relative to the maximal rate of change of flow

Regarding practical application of the method the ejection rate of change of power at the present time requires complex techniques and calculations However technical problems related to application of the method are being overcome Combination catheter tip velocity and pressure sensors are being tested An analog computer is being developed which will calculate the maximal rate of change of power from simultaneously recorded pressure and velocity Such a computer will cost approximately the same as an ordinary amplifier and will be utilized as a plug in device in combination with the catheter tip transducers and recorder Therefore with time the resources necessary for practical application of the ejection rate of change of power will be available In the interim we propose that the ejection rate of change of power merits further investigation The maximal rate of change of flow nevertheless is a useful index of performance which at the present time is more readily measurable

Regarding noninvasive applications the ejection rate of change of power has potential in this regard The combination of instantaneous flow and pressure potentially can be obtained noninvasively or semi invasively through ultrasound (as indicated by Drs Harrison and Smith) in combination with noninvasive or semi invasive analog pressure sensors which we are developing Noninvasive methods for the evaluation of ventricular performance would be advanta

Books received

Monitoring Heart Rhythm By C P Summerall III J Mangiaracina and J McNeely New York 19 6 John Wiley & Sons, Inc 208 pp Price $7 95

Venous Thrombo-embolic Disease Edited by C V Ruckley and I M C Macintyre New York 1975 Churchill Livingstone, ... pp Price $1...

My Favorite Heart Attack By Byron Thomas, Taftsville Vermont, 19 6 The Countryman Press, 33 pp Price $? ...

Child in Sport and Physical Activity Edited by J G Albinson and G M Andrew Baltimore 1976, University Park Press 233 pp Price $16 .0

Intensive Care Instrumentation By D W Hill and A M Dolan London 1976 Academic Press Inc 303 pp Price $21 25

Heart Attack By Louis S Levine New York, 1976, Harper & Row Publishers, 121 pp Price $6 95

Announcements

The Aachen and Munich prize

On the occasion of their 150th anniversary in 19 5 the Aachen and Munich Insurance Company in Aachen instituted the Aachen and Munich Prize for Technology and Applied Natural Sciences to be awarded every year with 60 000 Deutschemarks by an independent board of curators consisting of six professors of the Technical University of Aachen and the Technical University of Munich

This year the prize has been awarded to Rune Elmquist and Åke Senning, who were the initiators of the implantation of electric cardiac pacemakers and the prize is given in recognition of the great humanitarian importance of their fundamental progress in heart therapy The technical development was provided by Dr Rune Elmquist Swedish doctor and technologist. Professor Dr Åke Senning surgeon and at present director of the Surgical Clinic of the University of Zurich, was the first to implant the pacemaker in 1958 Both winners have developed one of the most productive therapeutical methods which represents one of the greatest achievements in medical progress over recent years

As a result hundreds of thousands of patients all over the world now owe their lives to the pacemaker It not only increases their life-expectancy but also improves their quality of life to a level that could not have been achieved by treatment with drugs. The patient notices the pacemaker so little that at times he completely forgets his life depends on the well functioning of this technical device The pacemaker therapy is a classical example of the benefits that arise from the close cooperation between engineering and medicine

Hypertension Task Force

The National Heart Lung, and Blood Institute (NHLBI) has announced the establishment of a Hypertension Task Force to evaluate the state of the art in hypertension research The NHLBI chairpersons and members are interested in receiving significant contributions from scientists in the various areas of research dealing directly or indirectly with the etiology and pathogenesis of the disease

The goals of the Task Force are to (1) assess our understanding and the gaps in our knowledge of the mechanisms of hypertension (2) determine among established research areas where greater emphasis should be placed to obtain new insights (3) elucidate promising areas of research which currently receive too little attention and (4) examine the extent and appropriateness of clinical applications of currently available basic information

The members have divided into several subgroups focusing on the different research areas To ensure active discussion from across the scientific community any ideas, recommendations, or comments which would assist the Hypertension Task Force and its work are welcome and may be addressed to the Executive Secretary Ronald G Geller PhD Chief Hypertension and Kidney Diseases Branch Division of Heart and Vascular Diseases, National Heart Lung and Blood Institute National Institutes of Health Bethesda Md 20014

Certification Examination in Subspecialty of Cardiovascular Disease

The American Board of Internal Medicine will administer the Certifying Examination in the Subspecialty of Cardiovascular Disease on Tuesday October 18 1977 Application forms for those wishing to take the examination may be requested beginning January 1 1977 and must be returned by March 15 1977

All inquiries concerning information and application forms should be directed in writing to Registration Department

Book reviews

***Decision Making in the Coronary Care Unit* second edition** By William P Hamilton M D and Mary Ann Lavin R N Saint Louis 1976 The C V Mosby Company 158 pages Price $6 50

This paperback practical compendium is designed for teaching CCU nurses and other CCU personnel It is presented as a series of case problems with electrocardiograms and other clinical background data The answers to the question What would you do? are not extensive enough for beginners since teaching is the primary objective of this publication There is a need to ask Why would you do what you would do? This is most important to a better understanding of therapeutic procedures For example the reasons and reservations concerning the use of carotid sinus pressure to stop paroxysmal atrial tachycardia should be clearly indicated in the answer to What would you do? Nevertheless the cases are practical and represent common problems encountered in the CCU This is a useful publication

Biochemistry and Pharmacology of Platelets CIBA Foundation Symposium 35 Amsterdam 1975 The Ciba Foundation 3o2 pages Price $23 95

This symposium held in London during January 1975 on platelets reviews in fair detail the biochemistry and pharmacology of platelets The recent interest in the role of platelets in clotting makes this publication particularly important and useful The range of subjects discussed is wide and fundamental The contributors present their data concisely As with all Ciba symposia the discussions are most interesting These discussions readily reveal the gaps in knowledge concerning platelet metabolism and function Cardiologists as well as pharmacologists biochemists and hematologists will find this book a valuable addition to their libraries

Vascular Surgery Edited by William H Edwards Baltimore 1976 University Park Press 257 pages Price $24 50

This short practical book on the surgical management of vascular disease edited by Edwards reviews occlusive disease aneurysmal disease arterial trauma thromboembolic disease and neurovascular disease in about 250 pages The contributors are from various vascular surgery centers of the U S A The discussions and approaches to the care of vascular disease are surgically oriented as would be expected but the medical or non surgical aspects are neglected This may be expected in such a short presentation Nevertheless on page 15 cerebral angiography is considered a safe method in diagnosis This is not entirely true since it is not 100 per cent safe The reactions to angiography are important to the patient who experiences them The cases described are almost all successful ones following surgery Those who are involved in non surgical fields of vascular disease know that the results of surgical care do vary especially with the experience and technical ability of the surgeon Regardless this book does clearly reflect very well the present attitudes concerning the surgical care of vascular disease

Human Malformations British Medical Bulletin Published by the Medical Department The British Council 65 Davies Street London 1976

The British Medical Bulletin is consistently a good publication Human malformations constitute an important problem in medical practice This publication which is mainly concerned with etiology and pathogenesis is not only important but should interest all doctors including cardiologists even though cardiac malformations constitute a very small part of the discussions Prenatal diagnosis role of drugs the environment chromosomal disorders legal problems and infective causes are among the subjects discussed This is a very good issue of the *Bulletin*

Thrombosis Platelets Anticoagulation and Acetylsalicylic Acid volume II Edited by Ephraim Donoso M D and Jacob I Haft M D New York 1976 Stratton Intercontinental Medical Book Corporation 200 pages Price $19 50

This small book of about 200 pages reviews very well selected aspects of the use of anticoagulants and the role and control of platelets in thromboembolic disease states The reader will find this to be a good condensation of the medical literature on the subject of thrombosis and the management of thromboembolic disease The book is clinically oriented and clearly defines present day practices in the use of anticoagulants and agents that prevent platelet stickiness This is a good sensible review which should interest all physicians in training and in practice

Organ Physiology Structure and Function of the Cardiovascular System 2nd edition By Robert F Rushmer M D Philadelphia 1976 W B Saunders Company 360 pages Price $10 00

Rushmer has made extensive and important contributions to teaching and research in hemodynamic physiology His book continues to be an outstanding contribution to cardiovascular physiology This paperback edition is well worth careful study by all physiologists and cardiologists These principles in the regulation of the circulation must be known before anyone can intelligently and logically treat heart disease Rushmer has put together in a clear concise and excellent manner some of the important physiologic phenomena for any reader who wishes to devote his time to learning the function of the circulation This is a very good publication

American Heart Journal

An international publication for the study of the circulation

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American Board of Internal Medicine 3930 Chestnut Street Philadelphia Pa 19104

Fourteenth Congress of the Pan Pacific Surgical Association

The Fourteenth Congress of the Pan Pacific Surgical Association will be held on April 1 through 7 1978 at the Hilton Hawaiian Village Hotel Honolulu Hawaii Concurrent meetings will be held in General Surgery Neurosurgery Obstetrics and Gynecology Ophthalmology Orthopedic Surgery Otolaryngology Plastic Surgery Thoracic Cardiovascular Surgery and Urology

For details regarding the Congress please write Cesar H deJesus M D Pan Pacific Surgical Association 236 Alexander Young Bldg Honolulu Hawaii 96813

National Conference on High Blood Pressure Control

The National Conference on High Blood Pressure Control will be held at the Great Gorge Resort Hotel McAfee New Jersey on April 17 through 19 1977 The conference theme will be The identified hypertensive patient Issues in long term medical management

The conference is seeking and will place highest priority on those research and practice papers that apply to the organization and methodology for achieving high blood pressure control for the hypertensive patient Abstracts must be post marked by December 15 1976 Inquiries and rules for submitting abstracts should be addressed to Conference Headquarters National Conference on High Blood Pressure Control 1501 Wilson Blvd Suite 600 Arlington Va 22209

Intensive Care Mechanical Ventilation course

The Department of Anesthesia in cooperation with Extended Programs in Medical Education University of California School of Medicine San Francisco Cal is sponsoring a postgraduate course entitled Current Problems in Intensive Care—Mechanical Ventilation This course is designed to cover theoretical and practical aspects of the effects and use of mechanical ventilation The course will be held at the Stanford Court Hotel San Francisco Cal on April 28 and 29 1977 The regular fee is $125 a half fee for non University of California house staff and postdoctoral students will be charged upon receipt of a letter of verification Advance registration is advised The program is acceptable for nine hours of Category I credit toward the Certificate in Continuing Education for the California Medical Association and the American Medical Association

For registration information please contact Extended Programs in Medical Education Room 569 U University of California San Francisco Calif 94143 Telephone (415) 666 4251

World Congress of Cardiology

The VIII World Congress of Cardiology will be held at the Hotel New Otani Akasaka Prince Hotel Tokyo Japan from September 17 through September 23 1978 The scientific program will include lectures symposia round table discussions free communications scientific exhibits and films The full member registration fee before May 31 1978 is $150 U S funds after June 1 1978 the full member fee will be $180 U S funds The family member fee before May 31 1978 is $80 U S funds after June 1 1978 the family member fee will be $100 U S funds Official travel agent for the Congress is Japan Travel Bureau Inc Convention Tours Section Foreign Tourist Department 1 13 1 Nihonbashi Chuo ku Tokyo 103 Japan The official carrier is Japan Air Lines Co Ltd For further information please contact Secretariat Organizing Committee VIII World Congress of Cardiology 7 3 23 Roppongi Minato ku Tokyo 106 Japan Telephone 03 401 1111 cable address is VIIICARDIOLOGY TOKYO

Author index*

July pp. 1 128 August pp 129-2 0 September pp 2 1 41 October pp 413-546 November pp 547 6 8 December pp 679-840

D

E

F

G

M

N

O

P

Q

R

S

Author index

Subject index*

C

D

P

U

V

T